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THE CONTRIBUTIONS OF BIOLOGY TO RADIATION THERAPY

JANEWAY LECTURE, 1957*

By SIMEON T. CANTRIL, M.D.
Tumor Institute of the Swedish Hospital
SEATTLE, WASHINGTON

ON THIS occasion of the first meeting of the American Radium Society beyond the borders of its country of origin, may I take the opportunity to express my appreciation for being honored to address you through the medium of the Janeway Lecture. It is quite fitting that this meeting brings us together in French Canada, since the influence of the French in the discovery and early investigations of radium had so profound an influence upon the development of radiation therapy. Dr. Failla, in his Janeway Lecture of 1939,[1] took occasion to remark upon "those accidental coincidences which sometimes determine subsequent events in a man's life." He alluded to the period when as a graduate student of physics his professor was a friend and neighbor of Henry Janeway, who was at the time interested in developing radium as a therapeutic tool, and was seeking the collaboration of a physicist. It was thus that Dr. Failla, somewhat by coincidence, became interested in radium and advanced from that beginning to make the very important contributions in radiation techniques, dosimetry and radiobiology which have had so quiet yet fundamental a bearing upon the direction of radiation therapy. May I also allude to a concidence which brought me as a youngster into the sanctum of l'Institut du Radium in Paris. Here I saw experimental radiobiology as laboratory investigation to elucidate clinical observation. Hence, I take this occasion to pay homage to those piercing, imaginative and, at times, unpredictable qualities of the French mind which through Messieurs Regaud, Lacassagne and Coutard influenced my perspective, not only in radiation therapy but in the general biologic concept of cancer.

In this era of a rapidly expanding interest in radiobiology we sometimes lose sight of the relative infancy of our science. Henry Janeway died of cancer in 1921 at the age of 47. He had only begun to develop interest in radium therapy. Following an

* The Twenty-second Janeway Lecture delivered at the Thirty-ninth Annual Meeting of the American Radium Society, Quebec City, Quebec, Canada, May 29–June 1, 1957.

earlier suggestion of Duane[2,3] he had, with Failla, gone far in perfecting methods of radon implantation of tumors utilizing glass seeds (1916–1925).* The development of gold seeds (1925) by Failla came as a result of Janeway's personal and painful experience with the necrosing effects of glass seeds when used in the treatment of his own disease.[1] Douglas Quick,[5] who was familiar with this early work and carried it forward, has subsequently remarked that "in our rush for shorter wave-lengths, a pause for reflection in retrospect might have been advantageous. This would seem an appropriate time for review of some of our older experience in view of the possibilities being opened up to us through production of various radioactive compounds."

To pose some doubt upon just how far we have progressed, one needs to read the early monograph of Janeway, Barringer and Failla (1917) on "Radium Therapy in Cancer."[3] We are still struggling with problems clearly stated then:

"It is one thing to know that the radiations have a differential effect on cancer tissue, and an entirely different thing to turn it to account successfully."

"In attempting to cure cancer by radium it must be recognized that not only is there an optimal dose of radiations for the cancer, but also that only small deviations from this optimal dose will make all the difference between success and failure."

Later before this Society, Janeway described interstitial radium dosage from the standpoint of volume, size, shape—a forerunner of the Paterson-Parker system in retrospect. Yet he concluded: "At the present it is dangerous to formulate rules.[6] The appropriate dose is solely a matter of judgment developed from experience."[2]

And again in bringing forth the closeness of our past, I call to your attention a study by Soiland presented before this Society in 1919.[7] It embodied a physical and clinical appraisal of variations between the action of the rays from radium and roentgen rays generated by "the ordinary set-up of a Coolidge tube, working on 100 K.V. pressure." There were then (as there are still) those who ignored one or the other agent in cancer therapy. He related that "it frequently happens that a roentgen operator with a most complete and efficient installation will deny any virtue whatsoever to radium, largely because he has been unable himself to secure any results from the capsule he bought in Paris or Vienna fifteen years ago. Again, we see Radium Institutes in which an almost unlimited amount of this precious element was available, where upon a dusty shelf could be seen a little old one-cylinder x-ray machine, which from time to time was aimed at a patient." The report was prophetic, in that it deduced that if ever one were able to utilize roentgen rays of a wavelength comparable to radium, the biologic and therapeutic effects would be similar.

The above brings us to restate the objective of the American Radium Society when it was founded in 1916: "To promote the scientific study of radium and other sources of ionizing radiation in relation to their physical and their therapeutic application."

To which might appropriately be added a phrase from Lacassagne.[8] "Sans aucune arrière-pensée d'humeur déplacé, on peut dire qu'en curiethérapie, plus qu'en toute autre matière, la façon de donner vaut mieux que ce qu'on donne!"

("Without intent of humor, one may say that in curietherapy, more than in any other matter, the manner of giving is of greater worth than that which one gives.")

And here it is timely for us to pay our respects to the passing of one of our oldest and most revered colleagues, George F. Pfahler, who died in January of this year of leukemia at the age of eighty-three. Dr. Pfahler was indeed a link with the past, yet he maintained an interest in the present and his life span represents the bridge between our recent origins and our uncertain future. Among many of his contributions, it is of interest to recall his animal experiments re-

* It is of interest that radon implantation was first suggested by Alexander Graham Bell in 1903.[4]

ported in 1906 in which for the first time use was made of silver, leather and aluminum as filters. He was impressed with the fact that the susceptibility to the rays varied in different animals and concluded that this was doubtless true for man.[9]

The subject which has been selected for review permits wide latitude of discussion. To attempt an understanding of the action of radiations on biologic materials has been likened to a man who tries to elucidate the mechanism of a telephone exchange by throwing bricks into it and observing some of the results (J. A. V. Butler). Radiobiology has quantitatively assumed proportions undreamed of prior to the dropping of the atomic bomb on Hiroshima. It is interesting to speculate where we would be if, instead of an atomic bomb with its devastating radiation injury, a weapon had been developed which was entirely chemical in its action, or perhaps had somehow exploited the shattering properties of ultrasonic waves. Such a coincidence would have channeled into other areas of science the vast effort now expended in radiobiology. The impetus given by the release of atomic energy is analogous to the rush of biologic experimentation in electricity or bacteriology when these had newly come within man's awareness. These natural phenomena have always been a part of man's environment. Yet it is in the nature of man that he seeks to understand, relate and eventually harness these forces to his ends. And so it is with nuclear forces and ionizing radiation. The urge to know is at this time, however, hastened by the realization that man cannot defy nature in creating a radiation environment greatly beyond that in which he has developed and which may therefore be unsympathetic to his continued healthy existence. It is fair to state that of all the natural and man-made environmental hazards to which we are subjected, radiation is better understood than most. Yet the gaps in our knowledge are wide, and we have only a pin-hole view of what some day may prove to be a fascinating panorama if we have the wisdom to curb the explosive potential of our discovery.

It is interesting to speculate how the concept of the release of nuclear energy could have been achieved in the period 1942–1945 had there not been the very substantial knowledge of radiation dosimetry and the injurious effects of radiation on man. This body of information had been accumulated in the previous three decades by relatively few workers in physics, radiobiology and radiation therapy. It formed the basis for the radiation protection program of the Manhattan Project without which it could not have progressed with the speed and safety which resulted.

In our busy routine of radiation therapy, we scarcely stop to wonder what is actually going on within the neoplasm and the host as he is irradiated. We are impressed with the potency of our radiation sources. Yet, in terms of total cellular, molecular and atomic composition of the body, it is startling to realize, as Gray has pointed out[10]—"That if a Methuselah were being treated for cancer and inadvertently left under the x-ray beam of a modern therapy unit day and night for 500 years, half the atoms in his body would still not have been directly affected by the radiation." And that "in terms of energy, one röntgen represents about 100 ergs/g. of tissue, so that a dose of a few hundred röntgens, which will kill many cells, is comparable with the normal energy requirement of a cell to carry on vital processes for one second or less."

Yet to those of us concerned with utilization of ionizing radiation in disease, and who have thus far been in quite profound ignorance of how, where and when our silent and invisible nostrum may act upon the patient, there arises the hope that we may gain practically in biologic understanding of radiations which may lead in time to more precise and less empirical application and increase the ratio of the useful over the unwanted reactions which so frequently lead to failure.

For a long period, with the one possible exception of Muller's observations on the

radiogenetic properties of roentgen rays, the main avenues of experimental radiobiology were conceived and initiated by observations made in applying radiations to the treatment of disease in man. And though radiobiology applied to radiation therapy is still carried on, this is not the immediate objective in the greater share of radiation studies now in progress. Ionizing radiation has become a very useful tool with which to study intricate biologic systems, as so well stated by Lacassagne: "Ce subtil agent de dissection des cellules consécutives des organs." Not a few of these relate to learning something of the mechanism of action of radiation, the better to protect ourselves from possible injury from our own (and others') experiments. In the rapidly expanding application of nuclear energy, technical achievements have far out-distanced our understanding of biologic action. And before man has learned to cope with his own radiation environment, he now proposes to jump off into outer space, where without doubt he will eventually organize an Inter-Universal Committee on Radiation Protection to protect himself from the cosmos.

It is timely for us to realize how much we are indebted to the physicists and engineers, and how comparatively recent are these innovations which we take so much for granted. My first experience with roentgen rays goes back forty years when I was fascinated as I watched the performance of a static generator, producing sufficient roentgen rays for my father to be able to see the broken bones of Wyoming cow-punchers. My introduction into radiation therapy was at a time when European radiology had just emerged from dosimetric methods utilizing colorimetric changes in various chemicals under irradiation (the forerunner of scintillation detection—and like so many discoveries, abandoned to be rediscovered under a new name). Röntgen in his second announcement had described ionization of air by roentgen rays and the method was used very early to measure radioactivity. As early as 1905, Franklin[11] of New York had devised an instrument to measure radiation dosage utilizing the principle of ionization produced in air. Villard (1908) first suggested a unit of measurement based on air ionization. A biologic dosimetry (erythema) replaced these early and promising objective dosimeters until the formulation of the roentgen in 1928. It is safe to state that at present the science of dosimetry far exceeds the preciseness of either our ability to achieve the desired dose in a specific volume of tissue or our powers to foresee its effect when this dose is approximated.

The physicists, chemists and engineers have supplied us with sources of radiation, electromagnetic and particulate, of any desired energy or range of action. Radioactive substances can be had in a wealth of energies and compounds. Yet, with all these additions to our tools, we seem to have reached a plateau of achievement. It does not seem that any startling events will come through the use of higher or lower energy irradiations, whether external or internal, than those now available. Of the many technical advances made during the past two decades one may cite (1) the perfection in dosimetry and (2) the availability of high energy roentgen and gamma radiation sources as the two most contributory to a small though significant improvement in the results of radiation therapy. If I may hazard a guess, it is that for external irradiation for cancer in general, the most useful radiations which will ultimately be sorted out of all the technical achievements, will be those which are in the range of the maximum gamma energies of radium. The name of our Society may well have meaning commensurate with its half-life. The radioactive isotopes have not as yet been fully exploited, and await more fundamental knowledge of the biochemistry of cancer before their possible selective use as internal irradiators can be realized. In 1927 Regaud and Lacassagne[12] expressed the concept that great good could come if means were found to localize exclusively within the malignant cell an irradiating

substance having a range of action of cellular dimensions. With the rare exception of iodine 131, specificity of deposition in cancer is not yet possible.

CONTRIBUTIONS OF RADIOLOGY TO BIOLOGY

As a primary consideration we may state that all ionizing radiations are injurious to man. In therapeutic radiology we produce varying degrees of injury, and by damaging some tissues more than others we attempt to salvage the patient. Observations of injury through ignorance or curiosity concerning the biologic properties of the newly discovered rays were the events which led to their therapeutic applications.

Alopecia incident to x-ray photography was described four months after Röntgen's discovery.[13] Dermatitis accidentally and experimentally produced came within a year after the advent of roentgen rays. Kibbe of Seattle (1897) gave perhaps the most authentic report upon radiation dermatitis experimentally produced upon himself, and, following the removal of a segment of skin, described the histologic changes both in skin and subcutaneous tissues.[14] We are familiar with the first biologic observation of radium from 0.2 gm. carried by Becquerel in his shirt pocket for six hours. This produced an erythema after an incubation period of fifteen days, followed by an ulcer which took a month to heal. A similar event occurred to Madame Curie and both Pierre Curie and Becquerel subsequently made experiments upon themselves. The similarity of certain physical properties of roentgen rays and radium and the potentiality and similarity of their biologic effects were soon recognized. The symptoms of acute radiation sickness were described in 1897.[15] The discussion by Béclère[16] of "mal des irradiations pénétrants" described the full syndrome of general radiation injury. Effects were principally attributed to an endogenous intoxication from cellular products liberated by the action of irradiation since many of the symptoms were independent of the site or the nature of the lesion treated. It was recognized that the severity was related to the area of the surface and total volume of tissue irradiated, the quantity of the dose absorbed, as well as the fractionation and protraction of treatment. It was likewise observed that the symptoms were inversely proportional in severity to the wavelength of the radiations used and diminished as the duration of treatment was lengthened.

By 1902 roentgen-induced cancer of the skin had been observed[17] and only seven years later 47 such cases were reported by one American surgeon.[18] Evidence of damage to tissues other than skin and proof of the penetrating character of the radiations was soon to follow. One of the earliest reported studies (1898) exploited the penetrability of the rays by exposing the spinal cord of small animals to a degree of irradiation producing severe cutaneous lesions and with resulting neuritis and paralyses. Histologic alterations were noted in the cord and meninges.[19] Belot, known as one of the foremost early French radiologists, authoritatively stated of these experiments at the time: "It is not necessary to believe that these anatomic effects may be produced in man; all these experiments have been done on small animals and one can establish no analogy between them and the human being."[20] (In the first of the animal experiments there was already concern about extrapolation to man.)

About the same time (1902) that *American Medicine*[21] published a clinical report on the great decrease in white blood corpuscles in roentgen treatment of breast cancer and abdominal sarcoma, Heineke in Germany reported his experimental studies of the effects of roentgen rays on the hemopoietic organs. The effects upon spleen, thymus, follicles of lymph nodes and intestine produced by feeble doses were explained on the basis of tissue in a high degree of cellular activity.[22] By 1911 there were 3 cases of leukemia reported as induced by irradiation and these gave the first alarm of more profound carcinogenesis than those of the skin.[23]

The observations of Albers-Schönberg[24]

on the action of roentgen rays upon the testicle (1903) were remarkable not only in that they demonstrated an effect of the rays upon an organ below the skin, but that this observation led to further studies defining a differential action of irradiation upon separate functioning tissues within the same organ. The observation of temporary or complete aspermia, depending on the time of exposure, was noted to be independent of the retention of potency. Following the work of Ancel and Bouin in France which elucidated the function of the interstitial cells, Villemin (1906) by irradiating the testes in animals was able to conclude: "X-rays are thus able to cause a dissociation between the two glands of the testicle. On the one hand they destroy seminal epithelium; on the other they respect the interstitial gland, confirming the experiments that the interstitial gland alone possesses a general action on the organism."[25] Here at an early date is irradiation as a biologic investigative tool.

Human experience in testicular injury was soon to be noted. Tilden Brown[26] of New York reported in 1905: "Men, by their simple presence in the neighborhood of a source of x-rays become sterile for a period of time which at present is indeterminate. None however has lost potency." A French comment upon this observation at the time by Roulier[20] is very much to the point—namely—had there been impotency, this action of the rays upon testes would have been discovered sooner. And we can also note the useful application of Albers-Schönberg's first experiments to radiation protection. In 1906, Laquerrière[20] described the plight of a young radiologist whose exposure to the rays began in 1900. In 1901 he was surprised to note that his mistress did not become pregnant. (The author hastens to assure us that she subsequently became pregnant by another partner.) In 1903, learning of the work of Albers-Schönberg, the young man traveled to Paris where he saw the use of bismuth rubber as a protective device and thus within five months his proved aspermia had departed and his wife became pregnant.

The classic studies of Regaud and Lacassagne[27] beginning in 1906 on the effects of irradiation on the testicle, with their completeness of description of differential effect upon the testicular elements, relationship of effect to stage of activity of the gland, influence of fractionation and protraction of dose on testicular and normal tissue injury and recovery, laid the foundations for successful radiation therapy.

As early as 1905 the extreme sensitivity of ovarian follicles to roentgen rays had been demonstrated, noting the lesser effect upon interstitial tissue, and the variation of effect with species differences and age.[28,29] Ovarian radiobiology was fully studied by Regaud and Lacassagne[27] with particular reference to the dynamics of follicle development and permanence of radiation injury which depended upon factors inherent both in the ovary and in the dose and protraction of irradiation. Of note also is the description by Lacassagne and Coutard[30] of latent follicular damage following nonsterilizing radiation, and the abnormalities of development which may ensue following fertilization. In this regard it is of interest that radiation damage to the developing embryo of the chicken was described as early as 1905.[31] An interesting experiment is reported by Tousey[32] in his text, "Medical Electricity and Röntgen Rays" (1910) in which he exposed a pregnant cat to "mild and short exposures," using his hands both to hold the cat and to judge the dose by erythema. The cat herself and the author's hands (at the time of writing) showed no ill effects, although the kittens were born dead. He rightly concluded with the warning only now being reiterated by our learned societies that "it is regarded as undesirable to make repeated radiographic or fluoroscopic examinations of the pelvis of pregnant women." Yet, as early as 1904 the treatment of a pregnant woman by massive irradiation given both externally and transvaginally for cancer of the uterus is reported by Laquerrière and Labelle[33] as noninjurious to the fetus. The midwife de-

scribed the infant in question as normal in all respects yet undoubtedly this poor unfortunate would belong in the group of malformed children described in 1929.[34] Such observations were all forerunners of the work of the Russells,[35] who analyzed the changing response of the developing embryo not only with dose but with the period of gestation, and the studies by Hicks[35] who described the effects of ionizing radiation on the developing nervous system. The culmination of these scientific investigations is, unfortunately, in the study of the outcome of pregnancy in women exposed to atomic radiations in Japan.[35,36,37]

It is not to be expected that our predecessors were any less curious about the biologic and possible therapeutic properties of the naturally occurring radioactive substances than are we who have the newly acquired radioactive isotopes for unlimited investigation. Hence, we should not be surprised to learn that most of the naturally occurring radioactive substances were used therapeutically with the disastrous results which we can now with hindsight blandly predict. The study of our past should engender caution, born of humility.

As early as 1904 techniques had been developed to expose animals to radon by inhalation.[38] The bromine salt of radium was shown (1906) to have the same ultimate deposition, regardless of its route of entry. By 1913 the naturally occurring radioactive substances had been studied from the standpoint of deposition, elimination and pathologic effects following intravenous injection. The techniques of autoradiography were beautifully demonstrated by Lacassagne and Lattès (1924) in their study of polonium.[39] Experimental production of cancer of the skin in animals (1918) and studies beginning in 1922 by incorporation of radium in gallstones and their insertion into the gallbladder with subsequent development of cancer were the first of many observations attesting to the carcinogenic properties of radioactive substances.[40] These investigations were given great impetus by the work of Martland (1925, 1929, 1931) concerning the development of osteosarcoma in dial painters. These latter studies, together with observations still continuing on the victims of the internal therapeutic administration of radium and mesothorium, are of great value to us today as a basis for estimating bone or other injury from deposition of long lived radioactive isotopes.

The foregoing examples are only a small segment of the rich clinical and experimental background of radiation therapy which was derived from observations of injury in man. Only two generations of physicians and scientists of diverse interests preceded us in a most remarkably thorough and imaginative description of radiation effects and interactions. In contemplating the far greater technical advantages of the present, and our inability as yet to push the understanding of radiation mechanism much beyond the frontiers reached by the last gener tion, we can all the more appreciate the magnitude of our inheritance.

We are aware that radiation therapy still largely relies for its guides on information derived from the patient. We may become impatient that progress is not more apparent and that we have not been able to profit more rapidly by the added richness of radiobiologic information and technical advances. In the space of some sixty years since the discovery of ionizing radiations, clinically oriented radiation therapy had its beginnings in the early 1920's. Technical progress in dosimetry and the engineering of the first supervoltage apparatus came in the early 1930's. Supervoltage irradiation remained relatively insignificant (and of questionable respectability) until the mid-1940's, since when it has become not only respectable but fashionable. *Yet evaluation by long term observation of results in selected forms of cancer remains the criterion by which its accomplishments and limitations must be judged.* And in the process we should not lose sight of the efficacy of medium voltage irradiation in a wide variety of neoplasms for which supervoltage therapy is neither necessary nor advantageous.

THE RADIATIONS

In looking for leads in which the action of ionizing radiation has in the past been usefully augmented by attention to biologic interaction and which have become fundamental tenets in radiation therapy, one comes first to *the differential biologic action of the radiations from radium* (and later of varying roentgen-ray energies and particle radiations). The early recognition of the three principal components of energy released by natural radioactivity preceded the experimental delineation of their varying biologic effectiveness. The first attempts to dissociate the biologic action of these different radiations began as early as 1901 in a study of their bacteriostatic effects.[41] The contrasting physical characteristics of the radiations pointed strongly in the direction of a varying degree of effectiveness. Early biologic studies and attempts to apply radium as a therapeutic agent developed the concept of filtration as a means to overcome the more caustic action of unfiltered radium as it was first applied. Dominici (1907) demonstrated that the superficial burn produced by radium could be greatly minimized by filtration with 0.5 mm. lead, permitting one to utilize rays which he described as "ultra-pénétrant" and having a more selective action deep within tissues.[41] Earlier mention was made of Pfahler, who in 1906 published his work on the filtration of roentgen rays.[9] The highly potent biologic effect of the alpha rays was early demonstrated by placing a drop of polonium in solution on the scarified ear of a rabbit resulting in rapid production of an ulcer leading to perforation.[41] This preceded by only a few years the recognition by Martland (1925) of the carcinogenic properties of alpha rays when radium was deposited in bones of dial painters. Early therapeutic use of fast neutrons by Stone[42] demonstrated still another differential effect of a new particle. The concepts of "specific ionization" and "linear energy transfer" had to wait upon the development of the cloud chamber and refinements in physical measurement. We have come to accept that there is a wide variation in effect upon similar tissues produced by an equivalent energy absorption of different types of radiation. Effects, as we are able to judge them, are similar in kind, but vary in degree. Biologic and particularly biochemical studies support the view that these quantitative variables are based upon differences in the mechanism of action. Alpha particles and neutrons produce greater nuclear disruption by direct interaction and are less influenced by chemical changes in the substrate than are radiations of lower ion density. Such observations may bear upon the more uniformly lethal effect of alpha particles and neutrons upon tissue regardless of alterations in their internal and external physiology.

Since there are these variables in biologic effectiveness with the character of the ionizing radiation, do we in present day radiation therapy turn them to useful account, or do they work against us? Experience with alpha particle therapy ceased after a brief assay with polonium and radium. Neutron therapy, in its only clinical trial to date, had an apparent rather too uniformly destructive effect upon normal and neoplastic tissue to believe it would have potential for wider exploitation. Other experiments with neutron and proton therapy are in the offing, and one cannot prejudge the outcome, except to remark upon the complexity of the physical arrangements required. High energy electron beam therapy is just now being realized. The question which arises to those now working with high energy roentgen and gamma rays is whether one should compensate for a lesser biologic effectiveness of these radiations as compared to that demonstrated for radiations in the range of 200 kv. Should the tumor dose utilizing 1–2 mev. roentgen rays or cobalt 60-gamma rays be increased over that which one formerly achieved with 200 kv. roentgen rays? The greater skin and bone tolerance and more sharply confined depth dose patterns of the high energy radiations are physical rather than biologic attributes. Experimental data with a wide variety of biologic media suggest that there is an effectiveness ratio for radiations in the

higher energy range which may be less by a factor of 0–10 per cent when compared to 200 kv. roentgen rays.[43] It would seem also that the imperfect state of our knowledge leads us to assume that this differential may or may not apply to all normal as well as neoplastic tissues. Our own experience of some twenty years utilizing roentgen rays in the range of 800–2,000 kv. leads us to the conclusion that any changes introduced by wavelength specificity are of lesser importance than those due to variation in the total irradiated volume, fractionation and protraction of dose. Of far greater significance are the gradations of radiosensitivity in tumors and within the same tumor. And more importantly, when patients are viewed now many years after irradiation, the progressive changes in normal tissue do not seem to be recognizably lessened for having been produced by high energy roentgen rays. The main difference is that one sees these late complications appearing in deep as well as in superficial structures. Hence, in supervoltage roentgen therapy we have not been influenced by considerations of relative biologic effectiveness (as compared with 200 kv.) in decisions concerning dose.

RADIOSENSITIVITY, PHYSIOLOGY AND CANCER

Biologic studies defining relative tissue *radiosensitivity* were the foundation for early advances in radiation therapy. In the first three decades following the discovery of roentgen rays and radioactivity, the relative vulnerability of normal tissues and the neoplasms derived from them had been learned, and little has been added to our knowledge thereafter. A limiting factor to further significant exploitation of irradiation in the treatment of cancer lies in our inability to as yet usefully increase the radiosensitivity of tumors or conversely to increase the radioresistance of important normal tissues. To a limited extent we have been able to manipulate radiation exposures in time to utilize physical qualities of radiation permitting us to take advantage of repair and thus augment the ratio of effect upon the neoplasm. Yet this is not equivalent to inducing a true alteration in radiosensitivity. It is conceivable that advances may come about which would: (1) alter an unfavorable radiosensitivity in the neoplasm; (2) provide the means to increase normal tissue radioresistance, or (3) increase the radiosensitivity of the neoplasm and normal tissues differentially in favor of the neoplasm; and (4) accelerate repair in normal tissues following irradiation. Radiobiology and therapy have provided clues which indicate that all of the above mechanisms are to some degree possible, even though not yet therapeutically achieved.

Radiotherapeutic experience has established that in general the radiosensitivity of a neoplasm is a function of its parent tissue. Chondrosarcoma has a radiovulnerability akin to cartilage, while lymphomas have a response commensurate with lymphoid tissue. Yet this concept is not wholly applicable, as witness the sensitivity of growing cartilage or the refractory state reached by some lymphomas. Within any variety of neoplasm there is a wide range of radiosensitivity, and indeed within the same neoplasm the vulnerability of its component parts, whether in the primary growth or its metastases, may vary enormously. The reasons underlying the variables may be sought in the cellular or vascular character of the tissue, or may be influenced by environmental factors which limit radiation injury. Zirkle,[44] in speculating on the cellular actions of radiations, has summarized present achievements by noting: "Whenever we carefully ponder the mechanism of any known radiobiologic action, we end by admitting that we have substantial direct information only about the very beginning and the very end of the story. The beginning is the act of irradiation . . . . The end of the story is the biological end effect . . . . These end effects are of such a nature that in no case have we been able to see how they can be directly related to the physical events constituting the beginning of the story."

There is a considerable knowledge of physical and chemical events related to actions of radiations. The quantitative trans-

fer of energy to the biologic medium and the mechanisms and distribution of energy transfer can be calculated and measured. Chemistry has described the formation of powerful oxidation—reduction radicals secondary to irradiation of aqueous systems. The complexity of the biochemistry of cellular components as they may be altered by radiation environment is becoming more evident as knowledge increases. Whether a biologic event is caused by the direct intervention of ionization or excitation of the molecules or whether the cause is an indirect one secondary to chemical intervention locally has still to be clarified for most events.

Are there indirect effects at a distance from the site of irradiation by intervention of circulating byproducts? Radiation sickness is evidence of such indirect mechanisms. The work of LeBlond[45] demonstrates secondary effects well beyond the site of irradiation, producing profound changes in thymolymphatic tissue, adrenals, stomach, intestines and liver. These give to irradiation a role comparable to other traumatic agents capable of inciting the reaction of alarm described by Selye.[46] The most common indirect effect of irradiation which we see daily is erythema. Yet the exact mechanism of its production is still unexplained. It is common observation that for a comparable dose the skin reaction of a large field is more intense than for a small field, and requires longer to heal. Reasons can be postulated for these indirect effects[47] yet the chemistry of the responsible agents is still lacking.

We somehow feel that our ignorance of basic mechanisms may be the key to our failures. In part this may be so, but since more generations will be required to unravel the puzzle, it would seem that for our foreseeable future we should seek to apply those segments of useful knowledge as they appear. In this respect there are two admonitions. The first is that all information relative to radiation effects has not been gleaned from clinical observation. And also we cannot expect our colleagues in science to furnish us with specific bits of information already tagged as applicable to therapy.

Radiation damage of the chromatin material of the nucleus, whether by direct energy release within the nucleus or by indirect interaction of chemical radicals in the cell or medium, leads to a series of events which may end in cell destruction or chromosomal alterations incompatible with continued mitosis or function. The review by Lacassagne and Monod (1922) of nuclear abnormalities provoked by irradiation and their observations calling attention to the rapidity with which these disturbances become manifest even during irradiation is as graphic evidence as has been portrayed of the disruption of nuclear division and the resulting changes which ensue with time.[48]

Advances in cytochemistry and particularly as they bear on nuclear injury have sought to explain the role of chromatin in cellular effects. These studies emphasize alterations in nucleoproteins (DNA, RNA) as the sensitive targets of injury. The concept that radiosensitivity is dependent upon the quantity of DNA has led to studies which show good correlation of known radiosensitive tumors with their measured DNA content.[49] Correlation is also found in quantitative differences of nucleoprotein in benign and malignant tumors, the poverty of which in benign tumors is postulated to be associated with the absence of invasion, lesser mitotic activity and other histologic signs of benign growth. There may also be a variability by as much as a factor of 20 in the relative greater abundance of nucleoproteins in the periphery as compared with the center of the neoplasm. This peripheral increase is associated with stromal influences, vascularity in particular. Gricouroff[50] has based a study of the radiosensitivity of migratory (metastatic) cancer upon factors of differentiation and DNA content of the nucleus. As the cell approaches senescence or differentiation, the DNA content declines. Detached malignant cells in the lymphatics, along nerve and blood vessel sheaths and in the skin, tend to be more differentiated and have a lower DNA content than do the

cells of the parent tumor or those outside the lymphatics but growing within the stroma or blood vessels. This factor may be in part responsible for the "acquired radioresistance" of tumors secondary to ischemia following irradiation, surgery or other influences limiting nutritional interchange.

Although the relative quantity of DNA in the nucleus in relation to radiosensitivity correlates with experience, refinements in histochemistry of nucleoproteins bring out complexities which point to the very incompleteness of our understanding. The role of precursors requisite to nucleoprotein formation, the sources and release of energy needed for mitosis and the many disparities of radiosensitivity in relation to mitotic phase and chromosomal activity may all somehow be pertinent to our problems. Yet it seems all the more baffling to apply these studies to human tissues and physiology in radiation therapy.

There are established observations in radiobiologic experience, however, which we cannot ignore. From radiotherapeutic experience we know that the radiosensitivity of a cell is not static, but changes with factors of development, cellular repopulation and function. Clinical observations support the evidence that those portions of a tumor which are well vascularized are the more sensitive, and that metastases from the tumor may have a radiovulnerability like or unlike the parent. Conceivably, there could be an increase in nuclear injury through biochemical intervention supplied before or during irradiation. We are seeking thus a chemotherapy which will render the nucleus more vulnerable by reason of nucleoprotein conditioning. As a nonchemist I have no suggestion other than to speculate. Whatever this complex state of the nucleoprotein may be, it exists inherently in a more vulnerable form in the nucleus approaching division than at rest; in the nucleus of the spermatogonia and not in the spermatid; in anaplastic carcinoma but not to the same degree in functioning secretory epithelium. I may add that I have great respect for the present advances in protein chemistry and it is not inconceivable that a more complete unraveling of the dynamics and alterations in nucleoproteins under irradiation could lead to a catalytic chemotherapy which would increase radiation effect on nuclear material. Nor do I underestimate the achievements in chemotherapy which have been able to inhibit biosynthesis of nuclear materials by an antagonist to a necessary nuclear component (*i.e.*, folic acid) producing remissions in acute leukemia of dramatic consequence.

This brings us to a brief consideration of another phase of cytochemistry which has now become a working tool in radiobiology. This concerns the concept of the formation of free chemical radicals by irradiation of water, their role in radiation injury and protection and in relation to the presence of dissolved oxygen and other solutes. Since man may be considered a compact aquarium of cells, this may have meaning in radiation therapy. When an hypothesis of radiation mechanism based on the indirect effect of free chemical radicals was first formulated as in part responsible for biologic action of radiations, an objection resulted from the enormous dosage required to produce these chemical products *in vitro*. The resolution of this dilemma is an example of the need to refine the methods of measurement in order to observe important effects hitherto unrecognized. The work of Dale (1942) which demonstrated the inactivation of pure enzymes in aqueous solution by irradiation with dosage within the therapeutic range gave importance and promise to this phase of radiochemistry.[51] Within the next year (1943) Dale *et al.* reported on the apparent loss of radiosensitivity occurring when enzymes were irradiated in the presence of various proteins which acted as protective agents by competing for activated radicals formed within the solution.[52] The application of this fundamental work to the later study of chemical protection from acute radiation injury has received renewed vigor with the vastly increased potential of radiation sources.

The formation of peroxides by interaction of radiation with water and partly in reaction with dissolved oxygen has been

stressed as another agent responsible for increasing biologic action. The amount of peroxide formed is dependent upon several factors, among which dose, quality of radiation and the concentration of dissolved oxygen have been demonstrated. That peroxides can be a factor increasing the occurrence of selective biologic events is generally accepted, yet the yield in ranges of dose used in therapy must be exceedingly small.

The role of vascularity and anemia in relation to radiosensitivity and the presumption that in this respect vascularity is synonymous with the oxygen supply to tissues was postulated from early therapeutic experience. As early as 1904 attempts were made to render the skin ischemic in order to decrease its reaction and permit a greater dose in depth. Compression, icing and local adrenalin injections were attempted.[53] A precise experiment by Schwarz (1909) demonstrated the reduced injury to skin when subjected to compression under irradiation. The effect was attributed to a lowered metabolism resulting from local anemia.[54] Clinical observation of the altered response of otherwise radiosensitive cancer was noted by Regaud in carcinoma of the skin developing in the scars of old thermal burns and in recurrences following irradiation or surgery. In 1914 Nogier and Regaud[55] published their observations on the diminishing effect of successive doses of radiation on cancerous tissue and likened the response to "radiovaccination." In 1920 Regaud[56] extended these studies to demonstrate that the progressive "radio-immunization" of a cancerous tissue developed parallel with the "radio-sensitization" of the vasculoconnective tissues and that with continued irradiation the end result was massive necrosis and cancer (described some twenty-eight years later by Paterson as the "supralethal dose"). Coutard early recognized that the prognosis by roentgen therapy was favorable in those cancers developing in a loose vasculoconnective tissue substrate with good vascularity (tonsil, base of tongue, exophytic epitheliomas) as contrasted with those which developed in and infiltrated dense musculofibrous structures with reduced vascularity (anterior pillar, oral tongue, pharynx).

The classic experiments of Jolly[57] and of Ferroux, Jolly and Lacassagne (1924, 1926) clearly demonstrated the marked diminution in the response of normal mammalian lymphoid and ovarian tissue when the blood supply was momentarily interrupted during irradiation.[58] Here was the first irrefutable experimental evidence of the effect of blood supply upon radiosensitivity. Mottram and Eidinow (1932), by irradiating a sarcoma implanted into the two flanks of an animal, demonstrated the variability of effect under normal blood levels and in the presence of anemia which was produced by bleeding.[59] The first experimental evidence linking oxygen deficit *per se* with reduced radiosensitivity was given by Petry (1923), who demonstrated a reduction in radiation effects upon growing grain shoots when their atmosphere was deprived of oxygen, and conversely the effect was augmented when these were irradiated while perfused in H_2O_2.[60] These were the forerunner of such experiments as described by Hollcroft, Lorenz and Mathews[61] showing the differential effect in transplanted lymphosarcoma in the mouse when 95 per cent versus 8 per cent oxygen was supplied during irradiation. Of interest to our problem of treating cancer metastatic to lymph nodes is the study by Trowell[62] showing diminution in sensitivity of lymphocytes in lymph node cultures *in vitro* with reduced oxygen. In lymph nodes containing metastatic cancer there could well be a lowered oxygen tension secondary to blocking of sinusoids and infestation by bacteria.

Lacassagne (1942), by obtaining survival of new-born mice when irradiated during complete asphyxia with otherwise lethal dosage, demonstrated the protective effects of anoxia *in vivo*.[63] He related the mechanism to earlier observations of Loisleur and Latarjet (1941) on the role of oxygen in completion of organic chemical reactions in solutions under the influence of

irradiation.[64] Dating from these experiments pointing to adequate oxygen supply through an intact circulation (1923–1924), numerous investigators have corroborated the role of oxygen by diverse experimental methods upon radiation effects in animals, insects, plants, bacteria, viruses, chromosomes and specific genes.

Discrepancy in the lack of oxygen effect in relation to increased radiosensitivity is noted only for heavy particle irradiation which may indicate that here the interaction may be largely within the sensitive zone of the nucleus and independent of chemical intermediates. Supporting this assumption is the almost complete independence of the presence of dissolved oxygen in the formation of H_2O_2 in aqueous solutions when irradiated with alpha particles, whereas there is such dependence with roentgen and gamma irradiation. Whatever the intricate cytochemical reactions may be, whether via oxidative intermediates or by direct interaction of free oxygen atoms, it seems clear that the presence of oxygen has a most important function in the initiation of radiolesions in biologic media.

The application of the influence of oxygen on radiosensitivity received clinical recognition long before the role of oxygen *per se* was established. The early recognition of the profound influence of local ischemia, of anemia and of infection as consumers of local oxygen is a manifestation of the recognition of the importance of the blood supply in radiation therapy. Fractionation and protraction, originally stemming from the work of Regaud on the relative radiosensitivity of cells during mitosis, were extended in principle by Coutard not only to take advantage of the achievement of higher dose with protraction but to complete the requisite dose before evidence of impaired circulation (edema, fibrosis) became manifest. This appreciation of the importance of vascularity led him to inject tumors with hydrogen peroxide prior to treatment long before the effect of this agent or free oxygen was demonstrated. That no appreciable good resulted may be due to a number of reasons, among them the short time interval (seconds) which has been demonstrated by Lorenz to be operative in bringing about an augmentation of tumor effect by irradiation following parenteral administration of hydrogen peroxide.[61]

The first report of which I am aware which attempted to observe the effects under irradiation of administration of pure oxygen to patients with cancer was by Hultborn and Forrsberg (1954) at the Radiumhemmet.[65] Irradiation of skin epitheliomas and adjacent normal skin by dividing the lesion and applying the same dose to each half while breathing either air or pure oxygen demonstrated a greater effectiveness both in the epithelioma and skin with oxygen consumption.

Basic to this entire study of oxygen tension is the whole problem of the development of a vascular system within tumors and the nature of the stimuli to blood vessel growth keeping pace with cellular division. Rapidly proliferating capillaries, known to the surgeon as proud flesh and to the pathologist as granulation tissue, could form the subject of a large body of research important to radiation therapy. What is the stimulus to its growth and could a capillary-inducing substance be found? Such studies as those by Merwin, Algire and Kaplan[66] demonstrating the inability of irradiated endothelium to produce new vessels, and the relationships between tumor regression or growth, and the function and growth of vascular supply are helpful to the understanding of radiation response as well as regrowth of viable tumor. They point up the precarious balance held by vascularity, both in augmenting radiation effect as well as nurturing uncontrolled foci following irradiation. Shapiro and Warren[67] have experimentally demonstrated the growth of nerve fibers in transplanted tumors and their vasomotor function in relation to nutrition and growth of tumor. Necrosis, infection, edema, thrombosis, as well as radiation damage all play a part in reducing oxygen supply. Microscopic studies

of epithelial tumors, devoid of capillaries except on the periphery, and in which the central cells must derive their nourishment by diffusion, indicate that the oxygen tension falls from 40 mm. Hg at the surface (corresponding to equilibrium with venous blood) to zero at the center for a thickness of only 150 microns. No central necrosis is seen in tumor cords with less than 160 microns radius from the stroma.[68,69] Such observations have important implications not only for oxygen in relation to cellular radiosensitivity, but are also correlated with the structural cytochemical (DNA) gradients from periphery to center of tumor nodules. Thus, a dose of radiation sufficient to kill cells at the periphery may end by leaving an increased nutrition for the remaining inner cells which aids in their recuperation and survival.

We are indebted to Gray *et al.*[68] for initiating and correlating studies preliminary to controlled human experiments in radiation therapy under increased oxygen tension. These demonstrate a similarity in pattern showing a rapid increase in sensitivity with irradiation which reaches a plateau rather suddenly when any further increase in oxygen fails to agument effect. The increase in sensitivity as measured by the reciprocal of dose is of the order of 2.5–3 which is the same conclusion reached by Patt[70] in a review of many experiments dealing with the protective effects of anoxia. The time factors required in animals to accomplish oxygen concentration affecting radiosensitivity are brief and of only a few minutes' duration.

The crux of the problem rests on whether normal tissues may be increasingly sensitized along with the neoplasm by a systemic administration of oxygen. Here Gray shows from experiment that a differential advantage may be gained by a greater increase in sensitivity of the anoxic tissue over those tissues already fully oxygenated, and that this differential may be as great as a factor of 1.5–2. This is demonstrated *in vivo* in mice inoculated with tumor, and breathing pure oxygen at one to three atmospheres. The effect upon the overlying skin was only slightly increased. It would be expected, however, that the normal tissue which was partially anoxic would be affected to a greater degree. The differential gain in sensitivity is related to a particular histologic structure and function and is not specific to neoplasia. In experiments described by Scott[68] in which tumors transplanted to the extremities were irradiated under increased oxygen tension, there appeared to be more bone necrosis. Further investigation of this phase (Howard-Flanders and Wright) demonstrated the increased injury to epiphyseal cartilage in the tail of growing mice by irradiation under oxygen respiration.[71] Of note here is that the cells responsible for growth are separated about 100 microns from the nearest capillaries and hence in their normal state of relative radioresistance may be under reduced oxygen supply. Of major importance in the experiments described by Scott relative to irradiation of tumor transplants under one to three atmospheres of oxygen was the observation that if the tumors were allowed to grow longer in order to reach larger size prior to irradiation, the oxygen effect was greatly diminished. Recently reported experimental studies[72] of the relation of tumor size in lymphosarcoma to dose required to control the transplanted tumors may be interpreted as evidence of vascular deficit. In both of these observations vascularity (or the lack of it) intervenes, and in its absence oxygen is not transported or diffused.

Radiation therapy of cancer in man under high pressure oxygen has been instituted on an experimental basis at St. Thomas Hospital, London, 1955.[73] The requirements for the safety and comfort of the patient under 3 atmospheres of oxygen within a pressurized tank are formidable when one considers the necessity for anesthesia to prevent convulsions which otherwise occur under high oxygen saturation and to relieve the apprehension and pain incident to puncture and maintained patency of the ear drums. Also, within the high pressure tank under anesthesia, the patient's respiration and cardiac function

must be indirectly recorded, with precautions against explosion under so unstable an atmosphere. Added to this are the technical details of irradiation, which first led to a single exposure of advanced cancer to doses of 1,000–1,500 r, purposely sublethal to tumor in order to better observe histologically the effects produced. The results have been sufficiently demonstrative of increased tumor effect with oxygen to warrant continuance of the experiments utilizing potentially curative doses. Out of this may come further knowledge of radiation effect upon human malignant and normal tissues which can have application in ways as yet unexplored.

In the meantime our discussion emphasizes the importance of attention to all factors related to adequate circulation and oxygen supply in radiation therapy. They point to preference for preoperative rather than postoperative irradiation when both are planned procedures in the management of a particular cancer. They give preference to surgery in the treatment of localized and ischemic tumors whenever possible. Support of impaired cardiac function, combating of anemia, attention to nutritional deficiencies, hemolysis and infection have in the past been recognized as highly important to tumor response.

Biology has provided us with most potent reinforcing weapons in the treatment of infections by the antibiotics. The steroids have been of very significant importance in the supportive therapy of patients with hemolysis and depression of hematopoiesis. These two contributions in themselves can be said to be among the important applications of biologic research to radiation therapy. Studies in progress on the use of transplanted marrow in hemopoietic replacement are promising of future applications. Of significance is the recent work by Jacobson on the influence of a powerful substance (erythropoietin) originating in the kidneys and triggering red blood cell production in response to oxygen requirements. These are but examples of the help which radiation therapy may unexpectedly receive from basic biologic research.

RADIOBIOLOGY AND MAN'S FUTURE

The increasing use of ionizing radiation in biology and medicine and the development of nuclear energy on a vast scale for a multitude of purposes make it incumbent upon us who share this responsibility to be increasingly aware of the potential danger which may result from the injudicious use of radiations in diagnosis and treatment of disease. Our profession requires that we also be informed on the possible injury which may accrue from environmental contamination by military and peaceful application of nuclear energy. This carries with it the responsibility to be informed concerning the actual status of the environmental hazards, how they are monitored and controlled and how sound (and at times how theoretical) are the bases for estimating the potential for injury either present or projected into the future.

We are becoming increasingly aware of the insidious carcinogenic properties of irradiation. A recent report by Warren[74] confirms earlier studies of a higher incidence of leukemia among radiologists. The mechanisms whereby carcinogenesis occurs may be variable. Both Failla[75] and Lacassagne[76] have recently considered the possible role of somatic mutations in cancer production by irradiation. Osgood's "unifying concept" correlates irradiation as one agent responsible for somatic mutation leading to malignancy.[77] In the causation of leukemia this would seem to be a more probable mechanism and unlike the process whereby late cancer develops secondary to ischemia and fibrosis of irradiation. Here the carcinogenesis would seem to reside in factors inherent in ischemia rather than in irradiation.[78] The synergism of factors related to bacterial infection and the induction of neoplasms in animals with doses as low as 600 r was demonstrated by Lacassagne (1929, 1933).[79]

An effect whereby irradiation adds to the wear and tear of all trauma of living is an acceleration of the aging process. First postulated from animal exposure, it is now being studied in man.

The effect of irradiation which is receiv-

ing increasing emphasis and study is the genetic alteration progressive with accumulated dose to the gonads. To date diagnostic medical gonadal exposure adds the largest increment to the 3–4 r received by the gonads from natural sources within the first thirty years. An appreciation of the importance of genetic injury as the most probable stringent factor in establishing permissible limits of external irradiation and induction of neoplasms as the most serious criterion for environmental contamination, point to the very urgent need for full pursuance of radiobiologic investigations to keep ahead of and yet be able to benefit by the advances in applications of nuclear energy.

CONCLUSION

Our discussion of biologic contributions to radiation therapy has by no means been complete. We may see, however, the outlines of a remarkably rapid application of the discovery of a powerful natural force both to the amelioration and potential augmentation of disease in man. The enrichment of radiation therapy and radiobiology has been by mutual exchange, but we are now more dependent than before upon a more complete understanding of the biologic interactions of radiations. Radiation therapy has served as a most useful agent in permitting us a better understanding of the natural history of cancer. It has had an important place in the treatment of this disease and will continue to hold this role until the fundamental biology of cancer is understood. We may expect from biology, biophysics and chemistry the eventual development of knowledge which may in part give greater effectiveness to our therapy, yet it does not appear to be in the nature of things that rapid advance can be anticipated. Some thirty years have been required to refine the observations of Minot on the relation of liver to pernicious anemia, which is about half the span since the discovery of ionizing radiations. Our problem is far more complicated, yet not hopelessly insoluble.

And here it is fitting to end by quoting from Regaud and Lacassagne:[80] "Les progrès de nos connaissances sur les causes de la radiosensibilité ont été lents, notre ignorance sur ce sujet est encore grande."

1211 Marion Street
Seattle, Washington

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ROENTGEN MANIFESTATIONS OF MALIGNANT MELANOMA

By THEODORE F. HILBISH, M.D.*
BETHESDA, MARYLAND

A REVIEW of the literature reveals that many articles have been written concerning melanoma* relating primarily to the clinical manifestations and prognosis. Isolated case reports are available describing the roentgenologic findings in selected areas; for example, the small intestine. A thorough study of reference material available, however, failed to yield a single report dwelling upon the diverse roentgen manifestations of this disease.

Because of a clinical research study of melanoma at the Clinical Center of the National Institutes of Health, an unusual opportunity was afforded to observe the roentgenologic changes associated with this disease. The primary purpose of this paper is to briefly discuss the interesting and, at times, unusual roentgen manifestations of melanoma. A few comments will be included concerning the clinical findings, prognosis and treatment.

CLINICAL FINDINGS

Melanomata may occur at any age but are rare before puberty.[21] Approximately two-thirds of all melanomata occur in patients over forty with the greatest incidence in the sixth decade.[12] The distribution of the lesions varies to some extent according to reports but there is general agreement that almost one-third of melanomata occurs on the head and neck, 20 per cent on lower extremities, 15 per cent on upper extremities, 20–25 per cent on the trunk with the remaining primary lesions occurring in the eyes, on the genitalia or other rare sites.[3,10] There is no doubt that the vast majority of lesions originates in the skin or mucous membranes. There are, however, numerous reports in the literature of other primary sites such as in the meninges, adrenal glands, intestines, etc.[5,7,8,16,17,19,25]

Experience indicates that any mole subjected to repeated trauma is a potential threat. If such a lesion increases in size or ulcerates, it should not be biopsied but treated as a malignant melanoma. A lesion too small to be noted by the patient or physician may terminate several years later in a rapidly fatal, widespread, metastatic process.

The prognosis of melanoma is poor. The majority of articles during the past three decades reflects a five-year survival of from 15–25 per cent.[6,10,24] Affleck records only a 10 per cent five-year survival.[4] Adair has been quoted as reporting a 33 per cent figure on the same five year basis.[2] A review of his article indicates that the 33 per cent five-year survival group included only primary operable cases,[2] in other words a selected group. Of a total of 267 treated cases only 38 patients or 14.5 per cent of the group survived five years. Thus, it is evident that a careful evaluation of statistical information must be made to determine reliability and to ascertain that common basic concepts are used to obtain the figures quoted.

In any event, it is quite evident that melanoma is one of the most malignant of diseases once it breaks through the natural local barriers and becomes widespread. The mode of dissemination is entirely unpredictable. The process may spread by local extension, through lymphatic or vascular channels or by all three avenues in a single case. The prognosis is directly dependent upon early recognition and proper treatment.

Metastatic lesions from melanomata most commonly appear within six months to two years.[10] "Delayed metastases"

* The term melanoma in this paper refers to the malignant variety of the mole and not the benign pigmented nevus.

* Chief, Diagnostic X-ray Department, The Clinical Center, National Institutes of Health, Bethesda, Maryland.

may occur fifteen to eighteen years after removal of the primary tumor.[3] Willis has reported a case with metastatic changes thirty-two years after surgery.[26]

TREATMENT

Many methods of treatment have been advocated throughout the years in an attempt to lower the discouraging mortality from melanoma. In the 1930's there were numerous proponents of radiation therapy. Ellis, for example, concluded that melanomata were definitely radiosensitive.[11] He attributed the failure of irradiation in many instances to poor general resistance of the patient or to changes secondary to old trauma and scarring. McEuen, in fact, in 1930 stated that surgery should be discontinued as the mortality was 100 per cent. He considered roentgen therapy with very high dosage as the method of choice.[18] Irradiation has been relegated to a minor role in the treatment of melanoma in recent years.

Other methods of treatment which have been advocated at one time or another include the local application of caustics, amputation of subungual lesions, Coley's vaccine, injections of drugs locally such as sodium arsenite, testicular removal[13,14] and electrodesiccation. The latter method has been mentioned only to be condemned as there is good evidence that this procedure causes dissemination of melanoma.

The consensus of opinion at present strongly favors radical local excision and regional lymph node removal.[1,2,6,10] Radiation therapy and other ancillary measures are reserved for those cases unsuitable for surgical treatment.

ROENTGEN MANIFESTATIONS AND REPORT OF CASES

This study was stimulated by the diverse roentgenologic changes observed in patients with melanoma under investigation at the Clinical Center. Representative cases have been selected to portray the roentgenologic abnormalities.

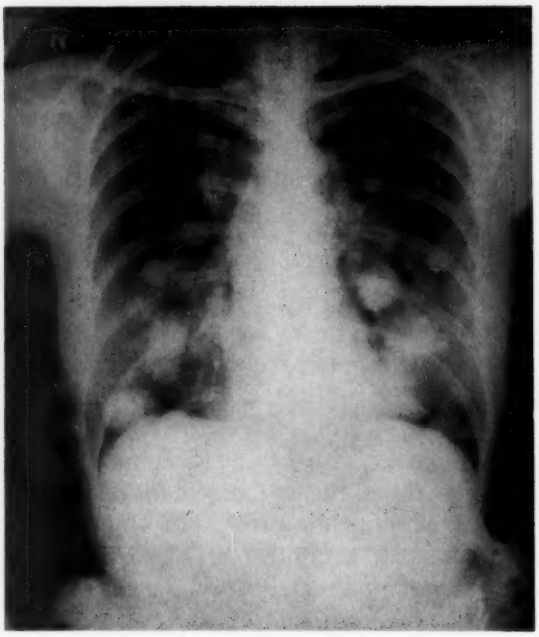

Fig. 1. Posteroanterior chest roentgenogram demonstrates multiple metastatic lesions of both lung fields. Lesions are sharply delineated and of varying size.

Case 1. H.M.S., a fifty-one year old white female, was admitted to the Clinical Center with chief complaints of weakness and fatigue of eight months' duration. A history of a pig-

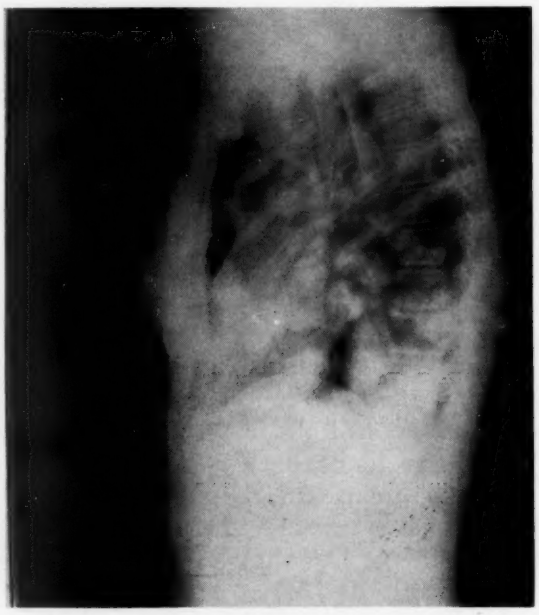

Fig. 2. Lateral chest roentgenogram reveals widespread distribution of lesions.

mented mole in the right temporal area present since birth was obtained. This mole began to grow in January, 1945 and was resected in February without microscopic study. The lesion recurred in July, 1950 and was removed with a histologic diagnosis of malignant melanoma. Local recurrences were excised and radical neck dissection was performed in October, 1953.

One year later widespread metastases appeared and the patient was admitted to the Clinical Center in November, 1954. Various forms of therapy were instigated without success. The patient's course was rapidly regressive and she died in January, 1955. Autopsy revealed multiple subcutaneous nodules, metastatic lesions in the brain and lungs and a terminal pyemia.

Roentgenograms demonstrated multiple large metastatic lesions in both lung fields (Fig. 1 and 2). There was also a metastatic lesion involving the left parietal bone (Fig. 3).

Comment. This case illustrates the most common type of metastatic change in the lung fields. The lesions are multiple, round, circumscribed and of varying size. They are not characteristic of melanoma as a very similar appearance may occur from metastases of chorioepithelioma, seminoma, sarcoma, etc. The metastatic lesion to the calvarium likewise is not characteristic of this disease. Wilner and Breckenridge reviewed 83 cases of malignant melanoma in an effort to evaluate bone metastases from this source.[27] They found that 10.8 per cent of their cases had bone metastases but state there was nothing characteristic of the lesions. This corroborates our experiences. Cases II and VII show metastatic bone lesions of different character.

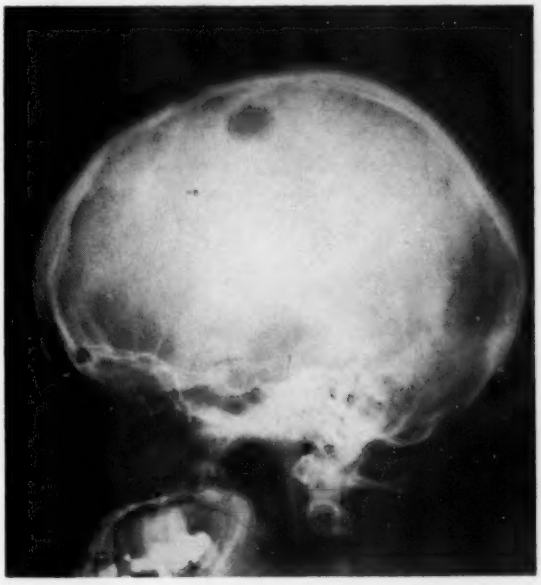

Fig. 3. Lateral skull roentgenogram shows sharply circumscribed metastatic melanoma of the left parietal bone.

Case II. O.B., a thirty-five year old white female, was admitted to the Clinical Center on June 1, 1954 with a chief complaint of intermittent pain in the left groin, buttocks, and leg. In 1953 the patient noted a nodule appearing in the center of a birthmark over the left upper abdominal wall. By July, 1953 the nodule was 3 cm. in size, firm and painful. Removal with prophylactic left axillary lymph node resection was accomplished in September, 1953 and the tissue study demonstrated a malignant melanoma. Pain appeared in the left leg shortly thereafter but destructive changes were not detected until roentgenograms were made of the pelvis in May, 1954.

Upon admission metastatic lesions were present under the left scapula, in subcutaneous tissues, pelvis, mediastinum and lungs. The patient was discharged at her request to return home on November 5, 1954.

Roentgenograms demonstrated metastatic lesions in the lung fields and mediastinum. In addition, there was an extensive destructive process involving the wing of left ilium, left acetabulum, and the head of the left femur (Fig. 4). There was a pathologic fracture of the pelvis with medial protrusion of the acetabulum and angulation of the left pubic bone at the symphysis.

Comment. This case demonstrates the extensive destructive change that may result from metastatic melanoma. A very similar roentgenogram was observed within one week of this case in which a large metastatic lesion involving the pelvis originated from the thyroid gland. Comparable changes have been visualized from breast metastases and multiple myeloma.

Case III. L.E.W., a thirty-three year old white male, was roentgenographed by the

Fig. 4. Anteroposterior roentgenogram of the pelvis demonstrates a large destructive lesion of the left ilium, acetabulum and femur. Note pathologic fracture.

Fig. 5. Left posterior oblique roentgenogram following a barium enema examination. Note infiltrative melanoma invading descending colon. Inset shows distortion of mucosal pattern as recorded on spot film.

author at a private clinic in Washington, D.C. in August, 1955. A barium enema examination revealed an infiltrative lesion involving the proximal descending colon (Fig. 5). An upper gastrointestinal study showed deformity and infiltration of the lower jejunum (Fig. 6).

Upon obtaining the patient's history, it was learned that in July, 1952 a tumor had been excised from the left parotid region and reported as a reticulum cell sarcoma. The patient felt well thereafter and for several months but during the ensuing three years lost 20 pounds in weight and developed intermittent constipation associated with abdominal pain which led to the roentgenographic studies mentioned.

An exploratory laparotomy in August, 1955 demonstrated extensive malignant melanoma with involvement of the omentum and the small and large bowel. The patient died in a Veterans Hospital on January 23, 1956 and an autopsy confirmed the roentgenologic and clinical findings. A review of slides of tissue from the left parotid lesion (1952) was reported by three separate pathologists as showing malignant melanoma.

Fig. 6. Upper gastrointestinal roentgenogram reveals infiltration and distortion of distal jejunum.

Comment. This case represents an example of melanoma invading the intestinal tract. There have been several reports of melanoma of the small intestine and, according to Wade, melanoma of the small bowel is extremely rare.[25] He was able to find only 9 cases of primary and 21 cases of metastatic melanoma invading the small bowel up until 1945. Katz, in 1950, reviewed the literature and added an additional case.[15] He likewise commented on the rarity of this lesion. Melanoma of the colon is even more uncommon than the small intestine.

Case iv. E.M., a sixty-five year old white male, was admitted to the Clinical Center on June 30, 1955 with the chief complaint of pain in lower abdomen, nausea and vomiting. Five years prior to admission it was noted that a mole on the dorsum of the right third and fourth toes had turned black in color. There was no increase in the size of the lesion until nine months before admission when a concomitant swelling appeared in the right inguinal region. A biopsy of the toe and right groin lesions obtained in New Orleans revealed malignant melanoma.

On admission the patient had ptosis of the right eye, a palpable liver and spleen, and a 3 cm. bluish melanoma over the right third and fourth toes as well as a 11 by 14 cm. mass in the right inguinal region. The patient's course in the hospital was rapidly downhill and he died six weeks following admission. An autopsy was not obtained.

Roentgenograms demonstrated multiple metastatic lesions in the lung fields. Of special interest were the multiple lesions involving the bladder wall (Fig. 7).

Comment. This case illustrates metastatic melanoma invading the bladder wall. Without knowing the patient's history, the changes demonstrated could well be confused with bleb formation of the bladder which is occasionally seen in other conditions. McComb and Smith reported a case of metastatic melanoma of the bladder as early as 1933.[17] They were able to find only four references relating to melanosarcoma of the bladder. The rarity of this lesion is further exemplified by a report of Stirling and Hunter in which they state that no metastatic lesions to the bladder were recorded in 3,000 cases of melanoma in the tumor registry.[22]

Fig. 7. Anteroposterior pyelogram. Note multiple filling defects of bladder wall. Inset of bladder more clearly delineates the filling defects.

Case v. O.D., a twenty-three year old white female, was admitted to the Clinical Center on July 29, 1955 with complaints of a chest tumor of two years' duration and headaches of two months' duration. In 1948 a pigmented mole was removed from the left upper arm which histologically revealed malignant melanoma. An axillary lymph node resection was consummated six weeks later. The patient was well until June, 1952 when she developed substernal pain, dysphagia and right shoulder pain. She subsequently developed headaches and loss of eyesight.

During hospitalization, the patient was treated with nitrogen mustard, roentgen radiation, and supportive therapy with some symptomatic relief and was discharged to home.

Roentgenograms of the chest revealed a large tumor extending from the right hilus into the right lung. There was phrenic nerve involvement with paralysis of the right diaphragm (Fig. 8). The esophagus was compressed. An angiocardiogram showed invasion of the superior vena cava, right atrium and right pulmonary

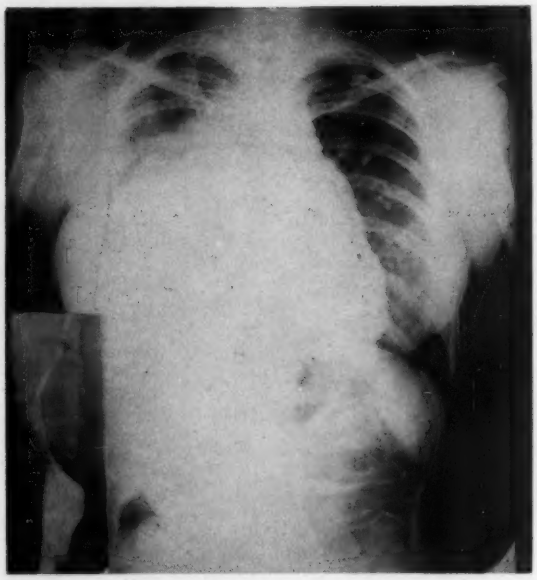

Fig. 8. Posteroanterior chest roentgenogram demonstrates a large mass extending from hilus into right lung field. The diaphragm is elevated. Inset shows compression of esophagus by extrinsic mass.

artery (Fig. 9). The latter vessel was almost completely obstructed.

Comment. This patient presented the clinical picture of the "superior vena cava syndrome," i.e., venous stasis, dusky color, etc. There are many causes of obstruction of the superior vena cava, but malignant melanoma is surely an uncommon etiologic agent. A tissue biopsy of the mediastinal tumor was not obtained, but the patient had a proved melanoma with axillary lymph node involvement and there was no reason to suspect other pathology.

Case vi. J.S., a thirty-six year old white female, was admitted to the Clinical Center on May 2, 1955 with the chief complaint of "boils" of three months" duration. A mole had been noticed by the patient on her left upper arm at the age of twelve. In August, 1953, during a second pregnancy, the mole increased slightly in size and became elevated. This was removed in April, 1954 by wide local excision in continuity with the left axillary lymph nodes. In February, 1955 a 3 cm. violaceous, recurrent melanoma appeared on the left shoulder. Since that date multiple lesions developed on the scalp, abdomen and thorax.

On admission there were melanomata on the chest wall, scalp, and abdomen of 0.5 cm. to 5.0 cm. in diameter. Local injections of potassium arsenite were given into some of the lesions

Fig. 9. Anteroposterior angiocardiogram reveals partial obstruction of superior vena cava with infiltration into right atrium and right pulmonary artery.

Fig. 10. Posteroanterior chest roentgenogram dated May 3, 1955 shows multiple metastatic melanomata in both lung fields. The largest lesion is paracardiac in location.

with decrease in size of control lesions. Since the latter part of May, 1955 until February, 1956, the skin lesions have entirely disappeared. Chest roentgenograms likewise revealed a regression of metastatic lesions.

One thousand cubic centimeters of blood were obtained from this patient for administration to other patients with melanoma. Two hundred and fifty cubic centimeters of whole blood were given to one patient without effect. The remaining 750 cc. of blood from the patient J.S. was separated into plasma and blood cells. The plasma was divided and given to 3 additional patients with melanoma—again without detectable benefit.

Roentgenograms on May 3, 1955 demonstrated multiple metastatic lesions in both lung fields. The largest lesion was located adjacent to the right heart border (Fig. 10 and 11). Subsequent chest roentgenograms dated December 19, 1955 showed a marked regression of the metastatic lesions. The peripheral lesions almost entirely disappeared and the paracardiac lesion decreased from 3.5 cm. in diameter to 1.5 cm. A lesion appeared, however, during the same time interval adjacent to the left hilus (Fig. 12 and 13).

Fig. 12. Posteroanterior chest roentgenogram taken seven months later (December 19, 1955) demonstrates marked regression of metastatic deposits.

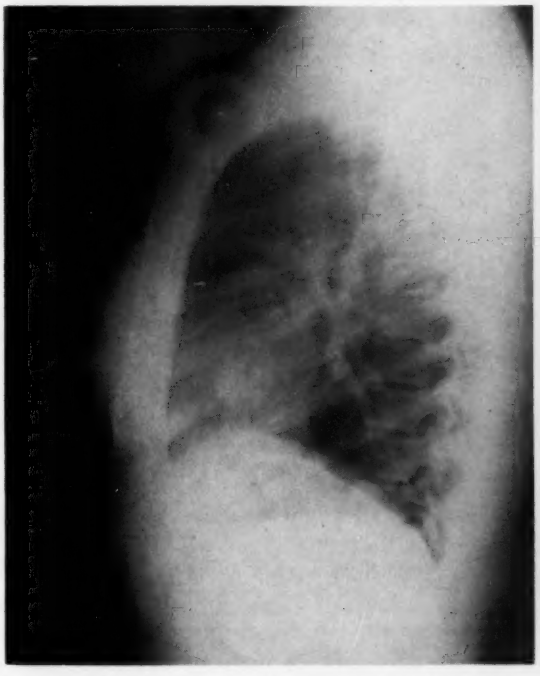

Fig. 11. Lateral chest roentgenogram same date (Fig. 10) more clearly portrays large paracardiac mass.

Fig. 13. Lateral chest roentgenogram of December 19, 1955 shows appreciable decrease in size of paracardiac lesion.

Comment. This case demonstrated the very interesting phenomenon of spontaneous remission of malignant melanoma. There have been a few similar reports in the literature.[9,20,23] No definitive explanation has been offered to account for the remission of these lesions, although there seems to be some relation to the hormonal status of the patients.

Case vii. M.T., a forty-one year old white female, was admitted to the Clinical Center on May 17, 1955 with a chief complaint of "lumps" on the skin of several months' duration. Three years prior to admission a raised area appeared in the middle of a birthmark on her right shoulder. One year later the lesion increased in size, bled, and shortly thereafter was excised with a resultant pathologic diagnosis of melanoma. The patient remained well until seven months before admission when cough developed and subcutaneous nodules appeared on various parts of the body.

Physical examination revealed lesions in the right groin, right deltoid area and left perineal region. There was also a metastatic lesion of the cervix which on biopsy was demonstrated to be malignant melanoma. Patient expired in July, 1955 shortly after aspiration of a pleural effusion. Autopsy confirmed the presence of melanomata in the areas detected clinically.

Fig. 14. Lateral gastrointestinal roentgenogram demonstrates anterior displacement of stomach and duodenum.

Fig. 15. Anteroposterior roentgenogram of left humerus demonstrates destruction of the lateral border of the shaft of the humerus with associated periosteal reaction and calcific deposition.

Roentgenograms showed a large metastatic lesion in the left lower lung field. There was anterior displacement of the stomach as demonstrated by gastrointestinal series (Fig. 14). Of special interest was the metastatic lesion involving the shaft of the left humerus (Fig. 15).

Comment. The roentgenologic changes consist of erosion and destruction of the cortex of the shaft of the left humerus associated with periosteal reaction and calcium deposition. Again a diagnosis of malignant melanoma would be quite unlikely if based on roentgenographic findings alone. As indicated in Comments under Case 1, there seem to be no characteristic criteria differentiating bone lesions of malignant melanoma from those of other sources.

Case viii. J.S., a fifty-eight year old white male, was admitteed to the Clinical Center on February 18, 1955 with a right hemiplegia and complete aphasia. In 1948 a melanoma was removed from the left deltoid area along with axillary lymph nodes. In November, 1954 the patient developed clumsiness of movements of the right hand and had difficulty in remembering names. In December, 1954 a left temporal

craniotomy was performed with removal of a metastatic melanoma. The patient improved temporarily but by January 23, 1955 there was recurrence of speech loss and right-sided weakness.

On admission there was bulging from the left temporal craniotomy as well as a scar from previous surgery in the left axilla and deltoid area. The patient was aphasic and hemiplegic. A second craniotomy was performed, and a portion of a large recurrent melanoma involving the left temporal lobe was removed. The patient's course was progressively downhill and he died on July 27, 1955. An autopsy showed metastatic melanoma in the left lung and pleura, spleen, tongue, adrenals, small intestines, and left temporal area of brain. There were gallstones present as well as a large bladder diverticulum.

Roentgenograms showed metastatic lesions to the left lung with an associated pleural effusion. An intravenous pyelogram demonstrated a large bladder diverticulum. A ventriculogram confirmed the presence of a large space-occupying lesion in the left temporal area (Fig. 16).

Comment. This case was included to show that melanoma may involve any structure of the body. The ventriculogram clearly demonstrated the presence of a space-occupying lesion proved to be melanoma. It is conceivable that the first symptom of melanoma might occur secondary to brain metastases as there are numerous case reports of widespread disease without a detectable primary source.

Case ix. R.F., a forty-two year old white female, was admitted to the Clinical Center on December 17, 1954 with nausea, vomiting and abdominal pain. A diagnosis of melanoma was established in 1947 when a mole of the left shoulder, present since birth, was excised, having increased in size. In March, 1954 epigastric pain developed. A partial gastrectomy was performed in June, 1954 following the demonstration of a neoplasm of the stomach by gastrointestinal series. Histologic study proved this to be a melanoma. Patient subsequently developed numerous subcutaneous nodules over the trunk.

During hospitalization her abdominal symptoms persisted. The patient's menses stopped in November, 1954 with an associated remission of the melanoma. In March there was a recur-

Fig. 16. Anteroposterior ventriculogram reveals a marked shift of the ventricular system to the right. The concavity of the left ventricle indicates the space-occupying lesion is located in the left temporal region.

Fig. 17. Posteroanterior gastrointestinal roentgenogram (March 22, 1955) shows ulcer crater high along the lesser curvature of the stomach. The incisura of the body of the stomach was secondary to previous surgery.

rence of menses with an associated reappearance of the melanomata. Patient developed obstruction of the stomach which was relieved by an operation in July, 1955. After recovery from surgery, she was allowed to return home but was readmitted to the hospital on September 23, 1955, semi-comatose, and died within two hours. Autopsy demonstrated melanomata of the liver, lungs, adrenals, kidneys, uterus and intestines. There was an enormous, solid, black tumor in the upper abdomen involving the stomach. An ulcer crater 7 by 14 cm. in size was present along the lesser curvature.

Gastrointestinal studies revealed a large mass in the upper abdomen compressing the stomach to the left. The first examination on December 10, 1954 demonstrated an ulcer high along the lesser curvature near the fundus. There was also a cone-shaped out-pouching of the mid-portion of the stomach due to previous local resection (Fig. 17). Subsequent gastrointestinal studies continuously demonstrated one or more ulcerations. There was also evidence of compression of the stomach with one persistent large crater along the posterior aspect of the lesser curvature (Fig. 18).

FIG. 18. Oblique roentgenogram (June 27, 1955) demonstrates extrinsic mass displacing stomach anteriorly and to the left. Note large ulcer crater on the posterior aspect of lesser curvature.

Comment. The roentgen findings were indicative of a large extrinsic mass invading the wall of the stomach with resultant secondary ulceration. There was symptomatic response to ulcer therapy, but at no time was there roentgenologic evidence of healing. Chandler and Jones reported a case of melanoma of the stomach which they thought to be primary in origin.[8] They were able to find 33 instances of melanoma of the intestinal tract, the majority of which involved the small intestine and were metastatic in origin. Melanoma of the stomach is indeed rare.

DISCUSSION

It is evident from the cases presented that diverse roentgenologic changes may result secondary to melanoma. The lesions may mimic changes occurring in many other disease entities. This is evident from our experience and has been commented upon by many authors. It is therefore important that radiologists be aware of potentialities of melanoma as far as roentgen manifestations are concerned. It is only when the proper etiologic agent is considered that the correct diagnosis is made.

The illustrations selected for this discussion reveal lesions of the skeletal, urologic, respiratory, neurologic and digestive systems. The most commmon lesions encountered clinically were melanomata of the skin. Roentgenologically, the most common manifestation was pulmonary metastatic disease.

SUMMARY

1. A brief discussion has been presented concerning the clinical findings of melanoma pertaining especially to location and prognosis.

2. Comment was made relative to methods of treatment. Radical local excision with regional lymph node removal is the treatment of choice.

3. The only hope for a reasonable cure rate seems dependent upon early diagnosis and prompt treatment.

4. It has been considered worthwhile to record this roentgenologic experience with

melanomata as a similar report is not available in the literature.

5. Selected cases have been presented illustrating the widespread and, at times, bizarre roentgen manifestations of this disease.

The Clinical Center
National Institutes of Health
Bethesda 14, Maryland

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RESULTS OF TREATMENT OF CARCINOMA OF LOWER LIP*

By SIMON KRANTZ, M.D.,† ISRAEL R. BERGER, M.D.,‡ *and* PIERPONT F. BROWN, M.D.§
ATLANTA, GEORGIA

THIS is a review of 189 patients with carcinoma of the lower lip treated at the Veterans Administration Hospital, Atlanta, Georgia, in the period of 1935 through 1950. The study was undertaken to evaluate and compare the results of irradiation and surgery. The initial mode of treatment in these 189 patients was as follows: 58 were treated by radium, 51 by superficial roentgen therapy; 18 received high voltage roentgen therapy and 62 patients were treated by surgery. Patients who developed recurrence or metastatic lymph nodes following this initial treatment were subjected to further irradiation or surgery.

In general, the type of treatment depended upon the period in which the patient was admitted to the hospital. The treatment from 1935 to 1941 was by radium in the form of a mold. After 1941, this method was replaced by superficial roentgen therapy, inasmuch as it was considered to be simpler and avoided the exposure of the radiologist to radium in the preparation and application of the mold. In this same period, 18 patients were treated with a high voltage technique in an attempt to compare and evaluate this method with the results obtained with superficial roentgen therapy. In 1947, with the establishment of a residency program in surgery, many of the patients were treated primarily by surgery. Although no attempt was made to select the specific type of treatment, patients with metastatic disease or those with a large lesion or invasion of the mandible were considered surgical problems.

Since there is a fairly equal distribution of the patients treated by these three modalities, that is, radium, roentgen therapy and surgery, it is felt that this offers an opportunity to compare and analyze the results of such treatment.

PATHOLOGY

Histologic confirmation was obtained in 161 patients. In the early period some lesions were not biopsied but were seen by at least two or three members of the Tumor Board, all of whom had had many years experience. It is doubtful that diagnosis was incorrect. The clinical diagnosis of carcinoma of the lip is fairly simple and there are very few conditions with which it might be confused. It is possible that keratoma or keratosis might be misdiagnosed as carcinoma, but there are those who believe that even these represent early malignancy.

In all except 1 patient the histologic diagnosis was squamous cell carcinoma. The exception showed adenocarcinoma. As has been pointed out by other observers,[3,6] the lip lesion is usually rated Grade 1 to 2 squamous cell carcinoma and rarely shows more activity.

SIZE OF LESION

The size of the lesion was indicated in the history of 173 of the patients. These are summarized in Table 1.

This table shows a fairly equal distribution of the various sized lesions treated by the individual methods. Fifteen lesions measuring less than 1 cm. in diameter were treated by surgery. Since this method pro-

* From the Departments of Radiology and Surgery, Veterans Administration Hospital, Atlanta, Georgia and Emory University School of Medicine, Atlanta, Georgia.
† Chief of Radiology, Veterans Administration Hospital, Atlanta, Georgia.
‡ Former Chief of Radiology, present address Athens, Georgia.
§ Resident in Surgery, present address Gainesville, Georgia.

Table I

SIZE OF LESION

Diameter of Tumor cm.	Radium Therapy	Superficial Roentgen Therapy	Deep Roentgen Therapy	Surgery
<1	2	6	1	15
1 to 2	24	30	4	17
2 to 3	12	18	10	6
>3	11	5	3	9
Total	49	59	18	47

vides excisional biopsy, it thereby gives simultaneously a diagnosis and a cure of the disease in this early stage. There are a number of patients listed under surgery who had previously received treatment of the primary lesion elsewhere, with the primary lesion apparently cured, but who presented metastatic lymph nodes on admission.

DESCRIPTION OF THERAPY

Radium Therapy. Radium available at this hospital consists of five tubes averaging 6.0 mg. and five tubes averaging 12 mg. These are of 1.5 cm. active length and have 0.5 mm. Pt filter. A mold of suitable contour to cover lip and chin was prepared. The radium-skin distance varied from 0.5 to 1.0 cm. The greater distance was used in bulkier lesions. The radium was so placed that the lip was crossfired from external, superior and internal aspects. This mold was left in place continuously (being removed for meals) for two to four days. The total dose given varied from 500 to 2,000 mg. hours.

Superficial Roentgen Therapy. The technique most often employed, and at present the accepted treatment at this hospital, was that of 140 kv., 0.25 mm. Cu. 1.0 mm. Al filtration at 16.5 cm. distance. Some of the lesions were treated with 100 kv. and 1 or 2 mm. Al filter. This technique can be used in small and superficial lesions. Daily dose varied from 400 to 1,000 r in air, depending on the size of the lesion—the smaller the lesion, the greater the daily dose. Total dose measured in air varied from 2,000 to 4,000 r. The larger doses were given when a longer fractionation of treatment was employed. An appropriate lead cut-out shield was prepared, covering the margin and at least 0.6 mm. beyond the margin. The mandible and teeth were shielded by lead covered with a rubber finger cot.

Deep Roentgen Therapy. Two hundred kv. therapy was used with the following factors: 0.5 mm. Cu and 1.0 mm. Al filtration; 50 cm. target skin distance; daily dose varying between 500 to 750 r up to a total dose of from 3,650 to 5,000 r in air. The same protection to surrounding healthy tissue and the mandible was afforded these patients as described above for superficial roentgen therapy.

Surgery. Surgical treatment was primarily directed toward complete excision of the lesion. The smaller lesions were removed by a "V"-shaped excision under regional or general anesthesia. Various types of plastic procedures employing the cheek or upper lip were used in patients whose wound did not lend itself to simple closure.

Routine prophylactic neck dissection has not been advocated or used in this hospital. It is felt, however, that in the presence of metastatic lymph nodes, the treatment is surgical rather than radiotherapeutic. Unilateral or bilateral neck dissections are determined by the location of the primary lesion, metastases and the extent of involvement. For example, a bilateral neck dissection for a midline lower lip lesion would most likely be carried out, even if lymph nodes were palpable on one side only. Where the lesion is localized to one side, unilateral neck dissection has proved adequate in the face of unilateral lymph node enlargement. With evidence of invasion of the mandible, a bilateral neck dissection with resection of the mandible and lip were performed at one sitting.

Those patients who clinically had definite metastatic lymph nodes, when first seen

with the untreated primary carcinoma of the lower lip were treated by surgery. In some instances when there was a question as to the true nature of the lymph nodes (metastatic or inflammatory), the primary lesion was treated by either irradiation or surgery and the patient carefully followed. If the lymph nodes persisted, a neck dissection was then performed.

Judging from experience, it appears that the metastatic involvement from carcinoma of the lower lip is different from that observed in intra-oral lesions. The process of development and extension appears to be much slower in the lower lip. It is for that reason that prophylactic neck dissection is not the practice in this hospital. Similarly, where a lymph node is small and there is a question of whether it is malignant or inflamed, immediate surgery does not appear necessary. If the patient can be carefully followed, he is kept under observation. When the lymph node persists after all the inflammatory reaction of irradiation or surgery of the primary lesion has subsided, a neck dissection seems warranted. As shown below, even in the face of metastatic disease, a great proportion of these patients can be salvaged with neck dissection. Careful histologic examination following such surgery has indicated that the disease remains fairly well localized and does not spread to other lymph nodes as in the case of intra-oral cancer.

RESULTS OF TREATMENT

In Table II it is shown that the relative cure rates of the initial treatment were 86 per cent with radium therapy, 88 per cent with superficial roentgen therapy, 85 per cent with deep roentgen therapy and 85 per cent with surgery in lower lip lesions without metastatic lymph nodes. These results are comparable to those reported in the literature by del Regato,[2] Howes and Rosenstein,[4] Ward and Betts,[10] and Widmann.[11] The absolute cure rates as noted in this table are rather low, 74 per cent, 74 per cent, 61 per cent and 79 per cent respectively for radium therapy, superficial roentgen therapy, deep roentgen therapy and surgery, but this is not thought to properly reflect the curability of this lesion. The total number of patients in the indeterminate group is rather large for the total number of cases. It is felt that the recurrence rate in these patients who were not followed would not be very high, since the disease is of rather low grade malignancy and the recurrent rate in those followed was quite low.

Results of Radium Therapy. With radium therapy there were 7 failures; 4 patients presented local recurrences and 3 developed metastatic disease without local recurrence. Of the patients with local recurrence, 2 were treated with additional radium and 2 by surgical excision. Two of these 4 patients later developed metastatic lymph nodes requiring neck dissection and 1 of these was not controlled by this procedure. Of the 3 patients who developed metastatic lymph nodes without local recurrence, 2 are well following neck dissection. The initial radium dose in the local recurrences was 350, 500, 1,230 and 2,300 mg. hours. Other cases treated with similar amounts of radiation for lesions of about the same size and appearance are free of disease. It is therefore difficult to state that the dosage and technique were inadequate in the patients with recurrence.

Analysis of the results as shown in Table II reveals a relative cure rate of 86 per cent and an absolute cure rate of 74 per cent from the initial radium therapy. If the end results are corrected by including those salvaged by further treatment, the relative cure rate becomes 96 per cent and the absolute cure rate 83 per cent.

Results of Superficial Roentgen Therapy. Five patients were considered as failures; 4 of these were local recurrences following doses of 2,000, 2,500, 3,000 and 3,500 r. With doses of over 3,500 r, there were no recurrences. It may be concluded that dosage in the order of 3,500 to 4,000 r, with techniques previously described, will yield

TABLE II

RESULTS OF TREATMENT

	Radium Therapy	Superficial Roentgen Therapy	Deep Roentgen Therapy	Surgery		
				Group I No metastatic lymph nodes	Group II Metastatic lymph nodes present	Total
Total Patients Treated	58	51	18	43	19	62
Indeterminate Group						
Dead as result of other causes, without recurrence	2	4	5	1	1	2
Lost to follow-up, without recurrence	6	4	0	2	0	2
Total indeterminate	8	8	5	3	1	4
Determinate Group	50	43	13	40	18	58
Failure of initial treatment in determinate group: recurrence and/or metastases	7	5	2	6	18	24
Salvage following further treatment	5	3	1	5	9	14
Died as a result of recurrence or metastases	2	2	1	1	9	10
Successful results						
Initial treatment only	43	38	11	34	9	43
Initial plus secondary treatment	48	41	12	39	9	48
Five year end results						
Initial treatment only						
Relative cure rate	86%	88%	85%	85%	50%	67%
Absolute cure rate	74%	74%	61%	79%	47%	63%
Five year end results						
Initial plus secondary treatment						
Relative cure rate	96%	95%	92%	97%	50%	83%
Absolute cure rate	83%	80%	66%	86%	47%	77%

excellent cosmetic results (Fig. 1–4) and practically no incidence of recurrence. It should be noted, however, that the recurrences with lower dosage were infrequent. For example, 6 patients received 2,000 r with only 1 recurrence; 5 received 2,500 r with 1 recurrence and 1 out of 4 receiving 3,000 r developed recurrence.

Metastatic disease occurred in only 1 of the 51 patients. This was four years after initial treatment, with complete control of the primary lesion. His disease, unfortunately, was advanced and palliative roentgen therapy was given without effect.

There was one other death in this group. This was a patient with recurrent disease, included in the recurrent cases that had further irradiation and surgery without control of disease.

Analysis of the results shows a relative

FIG. 1. Fungating carcinoma of lower lip.

cure rate of 88 per cent and an absolute cure rate of 74 per cent from initial treatment. Again, if those patients who were salvaged are included, the relative cure rate becomes 95 per cent and the absolute cure rate 80 per cent.

Results of Deep Roentgen Therapy. With deep roentgen therapy there were only 2 failures of initial treatment; 1 with recurrent disease that was controlled with further irradiation and the other with metastatic lymph nodes, there being no recurrence of the carcinoma of the lower lip. This patient died with disease. The relative cure rate was 85 per cent and the absolute cure rate 61 per cent. With further treatment the relative cure rate was increased to 92 per cent and the absolute cure rate to 66 per cent.

FIG. 2. Satisfactory cosmetic result after superficial roentgen therapy.

FIG. 3. Infiltrating carcinoma prior to superficial roentgen therapy.

In reviewing this type of treatment one is impressed with the low incidence of recurrence and the value in the rather advanced local lesions (Fig. 5 and 6). This technique is probably equally as good as that of superficial roentgen therapy.

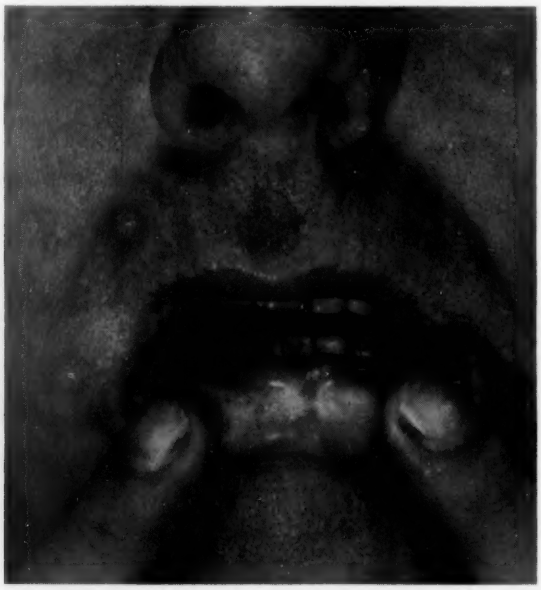

FIG. 4. Result after superficial roentgen therapy.

Fig. 5. Advanced lesion without involvement of mandible or metastatic lymph nodes.

Fig. 7. Recurrent carcinoma of lower lip following previous "V" excision and superficial roentgen therapy.

Results of Surgical Treatment. It is difficult to make a fair analysis of surgical treatment in comparison with radiation therapy since in the surgical group there are a number of patients who either presented advanced carcinoma of the lower lip with lymph node metastases or had had previous successful treatment of the lower lip lesion and were now admitted for treatment of metastatic lymph nodes. To establish a clearer appraisal, the surgical cases were arbitrarily divided into 2 groups. One group consists of patients with lower lip lesion only, the other of patients with metastatic lymph nodes. As shown in Table II, there was a total of 62 patients in whom the initial treatment was surgical. Of this group, 43 patients presented themselves with a lower lip lesion only; treatment was by surgical excision and the type of procedure depended upon the extent of the disease as previously described (Fig. 7–13). Thirty-three of these patients were controlled by surgical excision. Two were treated by fulguration. One of these died at the end of three years without any evidence of recurrent or metastatic disease—the other has survived five or more years. Two patients were lost to follow-up. Recurrence developed in 4 patients, 3 of whom are well following roentgen therapy. The fourth patient had many local surgical procedures without control of disease. Two developed metastatic lymph nodes and following neck dissection are now well.

If analysis is made, therefore, of these patients as was done with those receiving

Fig. 6. Result after deep roentgen therapy.

Fig. 8. Extent of surgical resection plus repair by upper lip flap.

FIG. 9. End result of surgical excision.

FIG. 10. Surgical excision of lesion involving entire lower lip, employing cheek flap.

FIG. 11. End result of this type of surgery.

FIG. 12. Advanced carcinoma of lower lip with invasion of upper lip and metastasis to cervical lymph nodes.

radium and roentgen therapy, the relative cure rate is 85 per cent and the absolute cure rate 79 per cent.

In the second surgical group there were 19 patients admitted with more advanced disease in whom the positive lymphadenopathy was a problem. There were 6 patients with metastatic lymph nodes only, the lower lip lesion having been apparently controlled by previous treatment elsewhere; the remaining 13 patients presented themselves with carcinoma of the lower lip complicated by metastatic lymph nodes. All of these had also had previous treatment elsewhere. It is surprising that following

FIG. 13. Cosmetic result following total excision plus upper neck dissection and repair by flaps from skin of chest.

surgical treatment, 6 of the 12 patients with lower lip lesion and metastatic lymph nodes are well and 3 of the 6 with metastatic lymph nodes only are well. One patient with a lower lip lesion and metastatic lymph nodes died two years later without evident disease. The results in this group were a 50 per cent relative cure rate and a 47 per cent absolute cure rate.

Analyzing the entire group of surgical patients treated, including those with or without metastatic disease, one notes a relative cure rate of 67 per cent and an absolute cure rate of 63 per cent.

Fig. 14. Ulcerated metastatic lymph node with invasion of mandible.

METASTATIC LYMPH NODES

In 34 patients, or 18 per cent, lymphadenopathy was present on admission. In 14 of these, surgery was instituted and all except 1 showed malignant involvement on histologic study. Twelve patients were thought to have inflammatory lymphadenopathy and were observed. Only 1 of these patients later was proved to have metastatic disease. This patient is well thirteen years following a neck dissection. Six patients had far advanced, inoperable metastatic lymph node involvement and were given palliative roentgen therapy. In the remaining 2 patients in this group, 1 was implanted with radon seeds and the other had roentgen therapy. There is no histologic confirmation of the lymph nodes in these cases but both are apparently well without further disease.

On the other hand, of the remaining patients, that is 155, who did not present lymphadenopathy on admission, only 8 developed metastatic lymph nodes later in the course of follow-up. Of these, some type of neck surgery was performed in 5 and local excision plus postoperative roentgen therapy in 1; the latter patient is living more than five years. Of the 6 surgical patients, 3 are living and well and 3 have died with disease. In the 2 remaining patients developing metastatic lymph nodes following initial treatment, the metastases were inoperable and no definitive treatment was undertaken.

It may be concluded from the above analysis, that the incidence of metastatic disease in carcinoma of the lower lip is fairly low. Eighteen per cent presented lymphadenopathy on admission but only 12 per cent had malignant disease. Of the remaining patients, only 5 per cent developed metastatic lymph nodes. This supports the theory that prophylactic neck dissection in carcinoma of the lower lip is unnecessary. It should be performed only when clinically demonstrable metastases are evident.[1,5,6,7,8,9] The present trend is away from prophylactic neck dissection.

Of the total of 25 patients who had metastatic disease, 11 are alive and well five or more years, 11 died of disease, 2 were lost to follow-up and 1 died without disease.

The treatment of metastatic disease is

Fig. 15. Result following radical neck dissection and partial resection of mandible.

TABLE III

TYPE OF TREATMENT AND RESULTS IN PATIENTS WITH METASTASES TO LYMPH NODES

	Total	Alive and Well	Dead of Disease	Dead without Disease	Lost to Follow-up
Roentgen therapy	9	1	7		1*
Radon seed implantation	1	1			
Unilateral upper neck dissection	3	2	1		
Unilateral upper neck dissection and excision of lower lip	3	1		1†	1
Unilateral upper neck dissection and resection of mandible	1	1			
Unilateral upper neck dissection and roentgen therapy	2	1	1		
Bilateral radical neck dissection and excision of lower lip	2	2			
Bilateral radical neck dissection and resection of mandible	3	1	2		
Unilateral radical neck dissection, contralateral upper neck dissection and excision of the mandible	1	1			
	25	11	11	1	2

* Less than one year.

† Died in two years of primary carcinoma of lung, no evidence of lip lesion.

summarized in Table III. The type and extent of the treatment varied with the stage and extent of the disease. A total of 8 patients presented inoperable metastatic lymph nodes. These were given palliative deep roentgen therapy and died with disease. One patient who was treated with roentgen therapy had a lymph node enlargement which was clinically considered malignant and, at the time of irradiation of the lesion of the lower lip, this was also irradiated. The lymph node enlargement regressed completely and the patient is free of disease for five or more years. Another patient presented a firm, metastatic lymph node that was implanted with radon seeds, due to the fact that he had a rather severe hypertension and it was felt that surgery was contraindicated. This patient is also alive five or more years.

In 15 patients, some form of surgery was performed. In 3 of these unilateral upper neck dissection was done and 2 of them are well; 1 died with disease. In 3, a unilateral upper neck dissection, with excision of the primary lesion, was carried out. One of these patients died of primary carcinoma of the lung two years after his lower lip was operated upon and at the time of death there was no evidence of recurrent disease. Upper neck dissection and partial resection of the mandible were performed on 1 patient; the patient is living and well. Unilateral upper neck dissection with postoperative roentgen therapy was used in 2 patients; 1 died with disease, the other is living and well. In 2 patients, bilateral radical neck dissection with excision of the primary lesion was considered necessary and both these patients are living and well. Three patients had bilateral radical neck dissections and partial excision of the mandible. One of these is alive and well. Unilateral radical neck dissection, contralateral upper neck dissection and excision of the mandible were performed in 1 instance; this patient is alive and well.

CONCLUSIONS

1. Treatment of the initial carcinoma of the lower lip by any of the accepted modalities yields remarkably uniform results.

2. The recurrence and incidence of metastases following initial, careful treatment is low.

3. Analysis of the results indicates that prophylactic neck dissection is not indicated.

4. In patients with operable metastatic disease, a 50 per cent cure rate may be anticipated with surgery. Our experience with patients having inoperable metastases is disappointing.

Simon Krantz, M.D.
Veterans Administration Hospital
5998 Peachtree Road, N.E.
Atlanta, Georgia

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ADENOID CYSTIC CARCINOMA OF THE ORAL CAVITY, PARANASAL SINUSES, AND UPPER RESPIRATORY TRACT

By MERALL ROTH, M.D.*
SAN FRANCISCO, CALIFORNIA

ADENOID cystic carcinoma has a gland-like structure similar to the cystic type of basal cell carcinoma. It is known by many synonyms, the most common of which is cylindroma. Other terms in usage are adenoid cystic basal cell carcinoma, adenocystic carcinoma, adenoid cystic epithelioma, adenocarcinoma arising in mucous glands, adenomyoepithelioma of cylindroma type, and pseudo-adenomatous basal cell carcinoma. Cylindroma is the oldest and most popular term, first used in 1859 by Billroth[3] in the description of a tumor of the maxillary sinus. Reference was not to the epithelial components of the tumor, but rather to the acellular hyaline columns which intertwined through it, bordered by epithelial or connective tissue cells. This concept has generally been lost by later writers who seem to think that the epithelial cells should conform to the name of cylindroma. Foote[8] calls it an adenoid cystic carcinoma (perhaps after Ewing), and this is the name we have adopted at our hospital.

Most of these tumors are in the major salivary glands, but many arise in the minor salivary or mucous glands found in oral and nasal cavities, paranasal sinuses, upper respiratory tract and bronchi. Some arise in the lacrimal gland, and others in the skin and breast. It is not known whether adenoid cystic carcinomas originate in the duct as Foote believes, or in the acinus. It is not a rare neoplasm.

Characteristically, the cells are small, fairly regular and darkly staining with relatively little cytoplasm. Mitoses are infrequent. They are arranged in cords containing tubular acini giving a Swiss cheese pattern. The lumens may be empty or may contain mucus, hyalin, or mucohyalin. Sometimes the epithelial masses are quite solid. Here the cells differ in size and shape, and some mitotic figures may be seen. The connective tissue stroma is variable in amount.

REPORT OF CASES

CASE 1. H.D. In 1940, at the age of twenty-three, this young white woman noticed a small nodule on the right side of her nose near the inner canthus of the eye. It became larger and after a year she went to a physician who took a biopsy (diagnosis unknown). She received three to six roentgen treatments and did not worry about the lesion. In 1943, the patient joined the Waves and served for two years. By 1945, the lesion had grown so that it partially obstructed the right nasal passage. A submucous resection was done which restored breathing space but left the swelling on the outside. An intranasal biopsy later that year was diagnosed as a cylindroma.

In 1946, when the patient first came to Stanford Hospital, the tumor extended to the inner canthus of the right eye, over the side of the nose, and on to the cheek for about 2.0 cm. The pathology was reviewed by Dr. Alvin Cox who thought the tumor probably arose in the ethmoid sinus. A tumor dose of 5,780 r (half-value layer 6.0 mm. Cu) was delivered in nineteen days in the hope of destroying the lesion and avoiding mutilating surgery. An acute reaction subsided satisfactorily and the tumor regressed remarkably (Fig. 1*A*). However, it recurred a year later and an excision of the right nasal-maxillary-palatal area was done, followed by a plastic repair which was immediately taken down when sections showed that tumor tissue had been left behind. In 1949, Dr. Dobson of Stanford Hospital persuaded her to go to Dr. Mohs in Wisconsin for chemosurgical treatment of the recurrence. Dr. Mohs thought he had reached a tumor-free plane, but ten months

* From the Radiological Service, Veterans Administration Hospital, San Francisco, California.

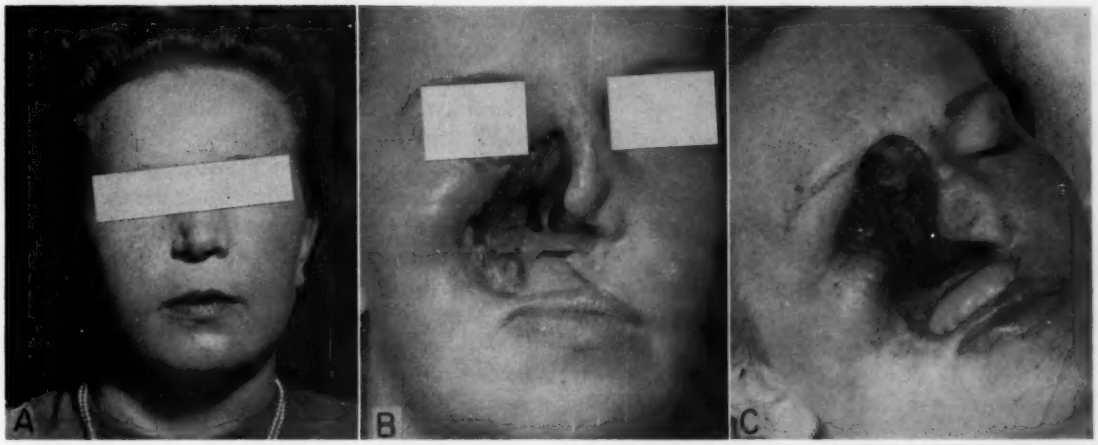

Fig. 1. Case 1. (*A*) 1946. After recovery from radiation effects of 5,780 r in nineteen days. The skin is somewhat atrophied. No tumor is evident externally. (*B*) 1949. Defect from surgery and chemosurgery. (*C*) 1950. Defect following more radical surgery.

later chemosurgery had to be done again by Dr. Shepard at Stanford Hospital for a small recurrence (Fig. 1*B*). Pulmonary metastases appeared about this time.

In 1950, the patient first came under our care. A radical resection was performed including removal of the right eye, and the right ethmoid and frontal sinuses, halting at the cribriform plate because of a cerebrospinal fluid leak (Fig. 1*C*). This was followed by irradiation with a Co^{60} spherical applicator of 6.0 cm. diameter of the surgical defect. The dose was 9,800 r at the surface in fifty hours. A year later roentgen therapy was administered to her lumbosacral spine for pain, although the suspected metastases were never proved. A tissue dose of 2,028 r in twenty-one days gave no relief.

The last admission was in September, 1952. Involvement of the eighth and twelfth cranial nerves had become evident. Narcotics were

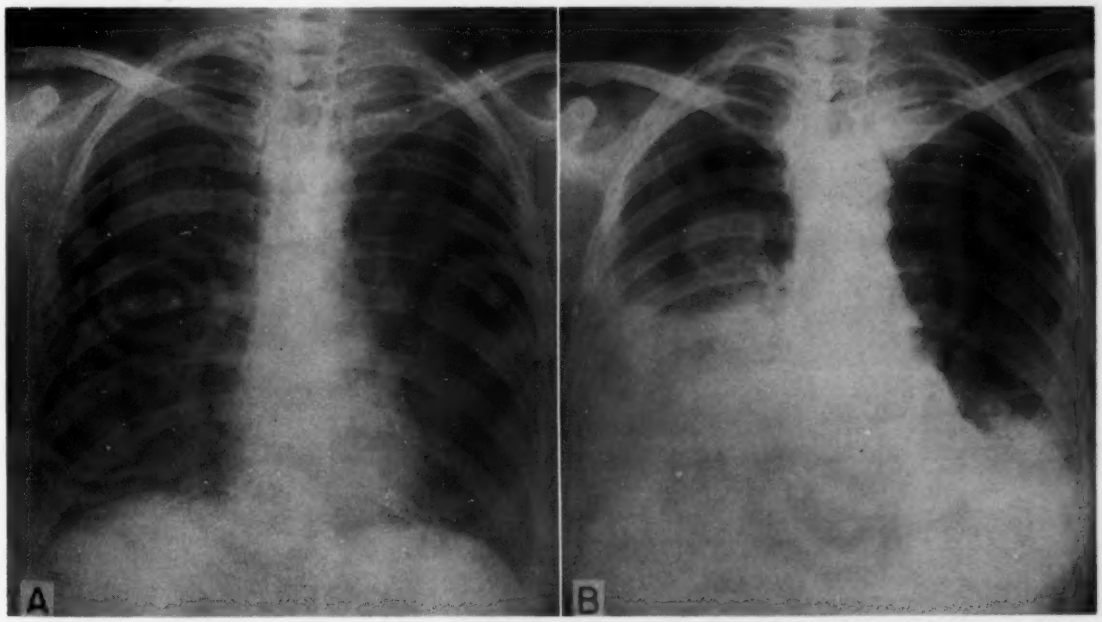

Fig. 2. Case 1. (*A*) January, 1952. Pulmonary metastases are seen behind the right first interspace, the left fourth rib and near the apex of the heart. Note shadow of unused pedicle graft. (*B*) September, 1952. The metastases are larger and there is pleural fluid bilaterally.

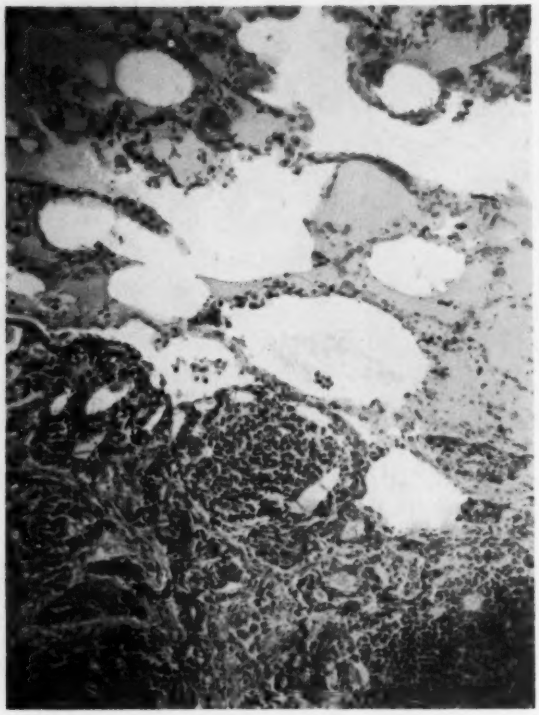

Fig. 3. Case 1. Pulmonary metastasis.

gradually increased to 1 grain of morphine every hour. Blood-tinged fluid was repeatedly removed from both sides of the chest (Fig. 2). The patient remained a pretty woman in spite of her disfigurement. She married during the course of her illness. She retained her courage and continued to dress her own wound until the day before she died on December 25, 1952, at the age of thirty-five, twelve years after the tumor first appeared.

At autopsy no local recurrence was grossly visible, but microscopically extension was demonstrated in the skull. Both lungs were filled with tumor nodules up to 5.0 cm. in size (Fig. 3). The pleura, pericardium, and diaphragm were heavily infiltrated by neoplastic tissue. A nodule was found in the liver and in one ovary. Infiltrations were noted in the lower pole of the right kidney, the adrenals, and the posterior lobe of the pituitary. No metastases were found to bone or lymph nodes. Examination of the brain revealed invasion of the right frontal cortex. The brain stem was not involved, but tumor infiltrated the lymphatics of the cranial nerves.

This case was included among 5 reported by Dr. Robert S. Pollack,[15] in 1952, while the patient was still alive.

Comment. This tumor arose in the right ethmoid sinuses and presented externally near the inner canthus of the eye, then advanced into the right nasal passage, cheek, antrum, orbit, and base of the skull. The local lesion was essentially asymptomatic until perineural invasion of cranial nerves occurred in the terminal phase.

The curative dose of irradiation is not known for this tumor. It is interesting to note that there was recurrence in the irradiated field after 5,780 r in nineteen days. Succeeding radical surgical procedures failed because of undefined extension beyond the borders.

Case II. J.R. This Filpino male came to us in 1949 at the age of fifty-five, with a 1.5 cm. nodule on the right side of the hard palate (Fig.

Fig. 4. Case II. (*A*) 1945. Tumor of the hard palate. The mucosa is ulcerated in the central portion of the mass. (*B*) Defect from resection of right maxilla and half the palate.

4*A*). This had been growing slowly for four years. Pain occasionally radiated to the right eye. After biopsy, the right maxilla and right side of the palate were resected (Fig. 4*B*). The pathologist called the tumor an adenocarcinoma, probably arising in a mucous gland and said it was incompletely removed. (Fig. 5, 6, and 7). Several attempts at grafting failed. A dental prosthesis was made to cover the defect.

After five years, the patient returned because of right facial pain. Recurrent tumor, proved by biopsy, was found in the antral area and was suspected of invading the inferior orbital plate. Because of its slow-growing character, we elected to preserve the eye, and surgery was limited to cleaning out the cavity for a cobalt applicator. A 141 mc Co^{60} source was fixed to the prosthesis (Fig. 8) and was placed in the defect for 161 minutes, repeated four days later. The estimated dose to the surface varied from 900 to 8,000 r. A bright erythema appeared the day after the second application and at the end of a week there was a second degree epithelitis with mucous patches. Necrotic slough formed in places within the cavity. By the end of two weeks, the epithelitis was subsiding but the

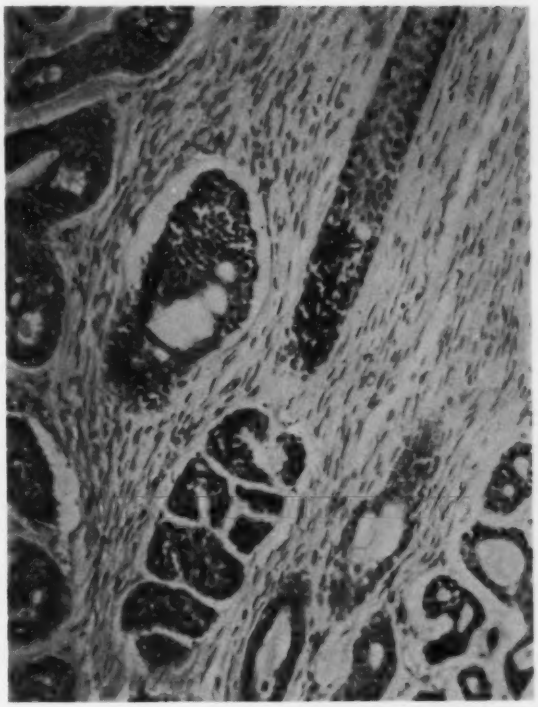

Fig. 6. Case II. Invasion of perineural lymphatics. Tumor is seen within endothelial lined lymphatic channels.

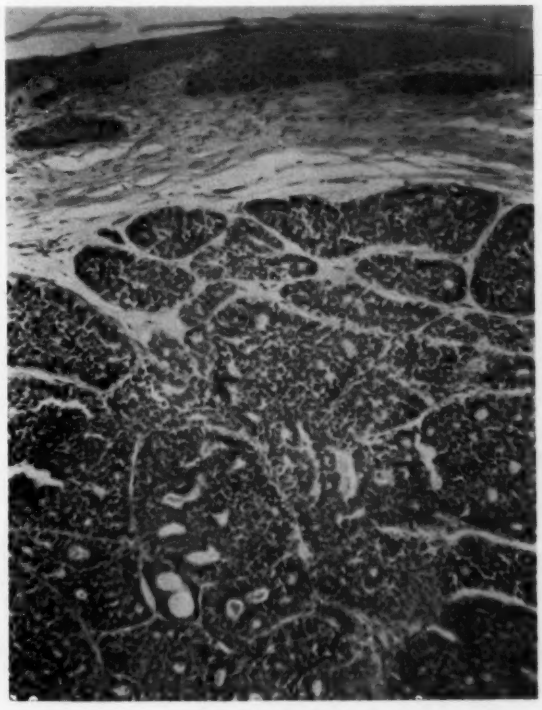

Fig. 5. Case II. Tumor of the hard palate. Numerous cystic spaces are seen in a cellular region. The connective tissue stroma is scant. The mucosa above the tumor is well preserved.

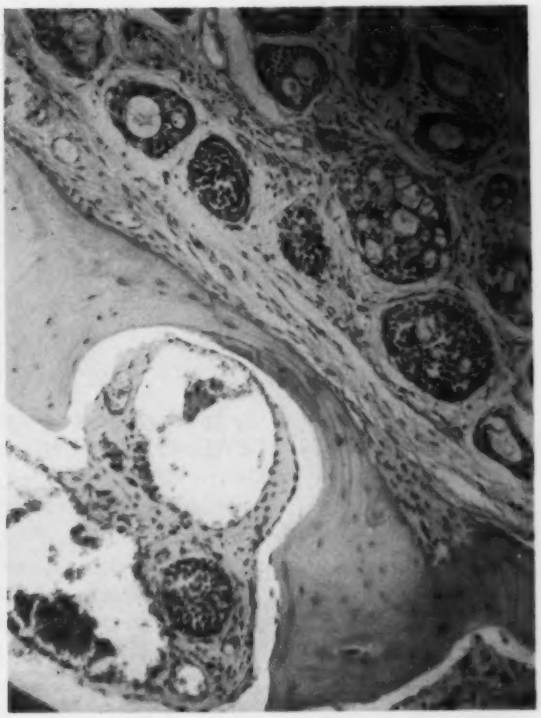

Fig. 7. Case II. Invasion of bone. The stroma is much heavier than in other parts of the tumor.

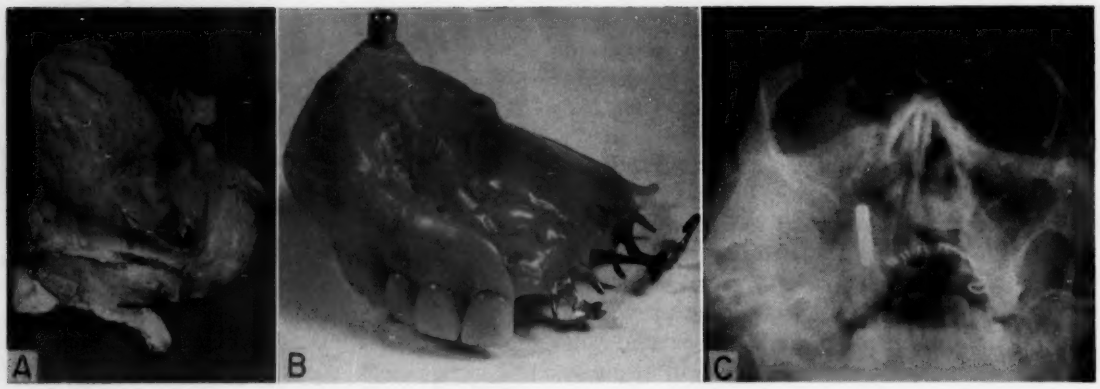

Fig. 8 Case II. (*A*) Mold on antral cavity used to plan placement of cobalt 60 and to calculate the dose. (*B*) Cobalt source mounted on dental prosthesis. (*C*) Roentgenogram showing the source in place.

slough increased. External roentgen therapy was started and a tumor dose of 5,000 r (half-value layer 3 mm. Cu) was delivered in seven weeks through 3 fields. By the second week of treatment a second degree epithelitis reappeared, and some of the necrotic material was beginning to separate away. A week later, the cavity was partly lined by grayish membrane. The epithelitis continued to progress elsewhere until a week after the therapy was completed. The reaction subsided during the next month, leaving clean surfaces partially covered by an atrophic membrane. Thirteen months later, in August, 1955, we saw no evidence of local recurrence. Ten years have elapsed since the tumor first appeared on the palate.

Comment. Although thirteen months is insufficient time to determine whether a cure or arrest has been obtained by combined external roentgen therapy and intracavitary Co^{60} therapy, we are gratified by the result in what appeared to be a hopeless situation. The relief of facial pain suggests regression of tumor infiltrating perineural lymphatics.

Case III. J.G. (Fig. 9). In 1942, at the age of thirty-one, while in the Army, the patient, a white male, had a sudden onset of dyspnea, wheezing, and productive cough, expectorating mucus and some blood. He was sent to Fort Lewis Hospital for suspected tuberculosis, but this was never found. After nine months, a bronchoscopic examination revealed a tumor of the lower trachea. This was removed bronchoscopically at Letterman General Hospital. The patient returned to full duty as a mechanic in a motor pool, leaving the Army in 1945. Occasional mild wheezing and coughing persisted, but the condition was essentially unchanged until January, 1954, when dyspnea and coughing began to increase. In July, he developed severe dyspnea, chills, and fever, requiring hospitalization and treatment in an oxygen tent. Shortly afterward he coughed up a plug of material. The dyspnea and other symptoms promptly disappeared and he went home. Later he began to cough severely when he ate or drank. Roentgenograms showed patchy infiltrates in both lungs, and tuberculosis was again suspected. He was sent to Livermore Veterans Administration Hospital where chemotherapy was started. A bronchoscopic examination was reported negative in September, but a month later there was narrowing of the trachea and paralysis of the left vocal cord. In November, a piece of a tumor that acted as a check valve, almost closing the trachea on expiration, was removed. This was called a cylindroma. Examination with barium swallow showed a stricture of the upper esophagus, indicating peritracheal extension. The patient was transferred to our hospital at the end of November. Although tuberculosis had not been proved we continued the chemotherapy.

Bronchoscopy showed a sessile, lobulated polyp on the left posterior wall of the trachea, extending from the carina to within 6.0 cm. of the glottis. At biopsy this was reported as adenoid cystic carcinoma. An episode of mild tracheal obstruction occurred in February, 1955, with dyspnea and wheezing. This was relieved by a bronchoscopic excision of a regrown tumor, and an indwelling tracheotomy tube. In May the patient began to complain of dysphagia. No gross tumor recurrence was seen in

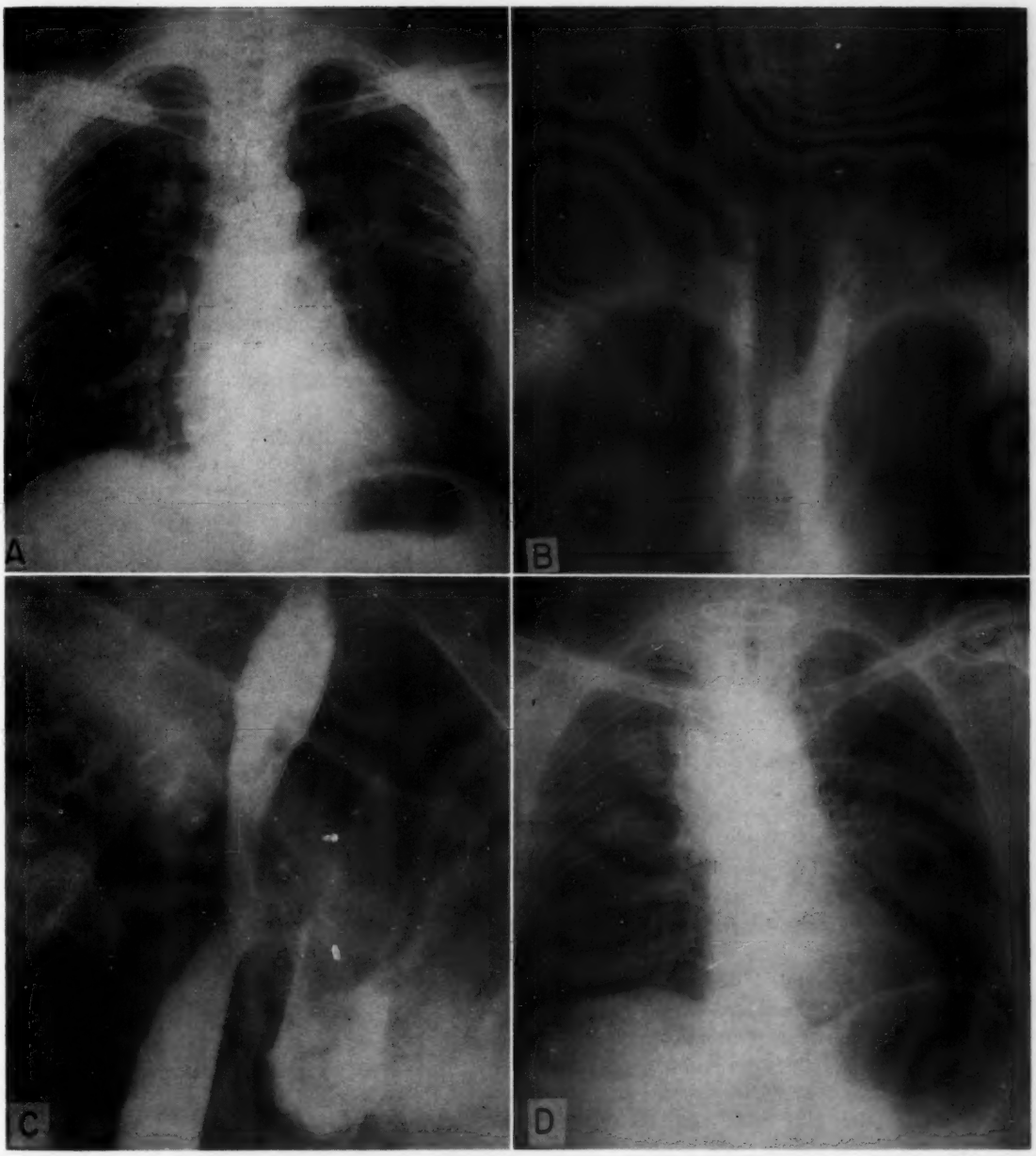

Fig. 9. Case III. (*A*) October, 1954. Multiple pulmonary densities suggest metastases, but could have been aspiration pneumonia. Tuberculosis was never proved. The trachea is narrowed in lower half (dotted outline). (*B*) January, 1955. Laminagram shows protrusion of tumor into trachea. (*C*) July, 1955. After 4,760 r in seven weeks, barium swallow shows narrowing of the esophagus and tracheo-esophageal fistula. The trachea is free of tumor. (*D*) September, 1955. Mediastinal widening due to peritracheal extension. The right upper lobe is atelectatic because of bronchial obstruction. Some of the pulmonary densities are larger, others are smaller. The left perihilar shadow is due to pneumonia.

the trachea. An esophageal tube was passed and kept there during roentgen therapy given through multiple fields. The tumor dose was 4,760 r (half-value layer 3 mm. Cu) in seven weeks. At the end of the treatments there was partial relief of the dysphagia. An esophagram demonstrated a tracheobronchial fistula although none had been present a year before. The indwelling esophageal tube did not entirely prevent aspiration, for cough continued, al-

Fig. 10. Case III. December, 1955. Metastases to the lower thoracic spine. Lead markers were used to locate the radiation field.

though dyspnea and wheezing were relieved. The patient went home but returned in August with chills and fever. This yielded to antibiotic therapy and was attributed to aspiration pneumonia. A milder bout of pneumonia occurred in September.

Early in August, the patient had moderate back pain, and slight collapse of the body of T-10 was demonstrated. The pain progressed by December, and there was a pronounced kyphosis due to collapse of three lower thoracic bodies (Fig. 10). Roentgen therapy with a tumor dose of 2,400 r (half-value layer 3 mm. Cu) in twenty-four days gave partial relief of pain. He was fitted with a back brace.

At the end of December, 1955, thirteen years after onset of symptoms, his dyspnea and dysphagia were controlled by tracheotomy and esophageal tubes; however, pulmonary and osseous metastases appeared and the patient's course was retrogressive. He was maintained on chemotherapy for suspected tuberculosis.

Comment. The obstructive symptoms are classical for tracheal neoplasm, and the course is characteristic for adenoid cystic carcinoma. The bouts of pneumonia were due to either blockage of the airway or to aspiration through the tracheo-esophageal fistula. Metastases can account for some of the pulmonary densities, aspiration pneumonia for others.

Case IV. C.B. This sixty-three year old white male came to us in May, 1955, with a small painful tumor on the roof of the mouth that had been growing slowly for a period of nine months. The adjacent right cuspid tooth had been removed without relief. The lesion measured 15 mm. across and was somewhat raised, firm, and centrally ulcerated. The patient's remaining teeth were carious, but none of them was near the lesion.

The alveolar ridge was resected, together with adjacent mucosa of the palate and buccal sulcus, to a distance of 0.5 to 1.0 cm. beyond the gross evidence of the tumor. A frozen section showed adenoid cystic carcinoma that had been cut across. Four additional strips of mucosa were taken from the hard palate. Each in turn showed tumor cut across at the margins and at the base. The attempt to reach tumor-free tissue was discontinued without resecting the soft palate or opposite alveolar process, since the histologic evidence suggested bone invasion and the possibility that the tumor extended beyond the soft palate and palatine arches. Three biopsies beyond the area of surgery taken two weeks later and four more after a month failed to demonstrate tumor. Roentgen therapy was begun two months after the operation, delivering a tumor dose of 3,500 r (half-value layer 3 mm. Cu) in thirty days through bilateral facial fields covering the hard and soft palate, and maxillary sinuses. A moderately severe epithelitis developed. The palatal mucosal defect had filled in satisfactorily with granulation tissue and was partially re-epithelized. After the acute reaction subsided, six biopsies were taken beyond the operative margins. These were all negative. The opinion persisted that tumor was probably still present, but no borders could be defined for a surgical procedure. After a lapse of three weeks, a second course of roentgen therapy was given, similar to the first, making a total dose of 7,000 r in three months. Severe epithelitis with mucous patches developed toward the end of treatment. By December, the only residual of the radiation reaction was a mild edema of the buccal mucosa.

Comment. This case illustrates the widely infiltrative character of these tu-

TABLE I

CASE REVIEWS

Author	Case	Sex	Age Initial Visit	Origin of Tumor	Extension	Metastases		Duration of Symptoms before Treatment	Treatment		Survival
						Antemortem	Postmortem		Initial	Recurrences	
Pollack[15]	1	F	33	Left antrum	Nasopharynx, pterygomaxillary space, orbit, anterior fossa of skull	Bones, lungs 6 mo., mediastinum		5 yr.	Radical resection of antrum and ethmoids, 5,061 r tumor dose	Exenteration of left orbit + 1,900 r and 2,000 r in air, using roentgen therapy through 2 fields	Alive, 7 yr.
	2	F	26	Left antrum	Left nose, hard palate, middle fossa of skull	Lungs 4 mo., pleura	Heart, liver, peritoneum, uterus, ovaries	3 mo.	High dose roentgen therapy and radical antrectomy		Dead after 6 mo.
Lampe and Zatzkin[13]	3	F	49	Right antrum	Right palate	Lungs, 3 yr.	Bronchial and mediastinal lymph nodes, pleura, spleen, liver		Surgery and radium	Roentgen therapy, partial resection of maxilla, 2,800 mg.hr. intracavitary radium	
Leonardelli and Pizzetti[14]	4	M	51	Antrum	Invasion of other sinuses			Several mo.	Excision and roentgen therapy	Electrosurgical dissection	Alive over 1 yr.
Lampe and Zatzkin[13]	5	F	33	Right maxilla	Right upper cheek, facial bones, temporal fossa	Lungs, 7 yr.			Excision	Multiple excisions, roentgen therapy, 3,000 r in air to 2 fields	Alive 15 yr.
Pollack[16] and Roth	6	F	24	Right ethmoid	Right nose, antrum, cheek, orbit, base of skull, pituitary, brain, cranial nerves	Lungs, 3 yr., pleura	Pericardium, diaphragm, liver, kidneys, ovary, adrenals	6 yr.	Roentgen therapy, 5,780 r tumor dose	Maxillary nasal palatal resection, chemosurgery, chemosurgery repeated, exenteration of right orbit, ethmoid and frontal sinuses + 9,800 r with Co^{60} applicator	Dead after 12 yr.
Pollack[15]	7	F	41	Left nose	Left antrum, orbit	Right ilium		15 mo.	Roentgen therapy, 6,000 r tumor dose	Ethmosphenoidectomy and radical antrotomy plus 3,000 mg.hr. intracavitary radium	Dead after 5½ yr.
	8	M	29	Left posterior naris, and nasopharynx	Left antrum	Lungs		1 yr.	1,000 r roentgen rays, radical antrotomy, 5,000 r γ radium		Alive 2 yr.

TABLE I (*continued*)

Author	Case	Sex	Age Initial Visit	Origin of Tumor	Extension	Metastases		Duration of Symptoms before Treatment	Treatment		Survival
						Antemortem	Postmortem		Initial	Recurrences	
Albrecht[1]	9	F	47	Right hard palate	Right alveolus				Excision and roentgen therapy	Roentgen therapy	Alive 7 yr.
	10	M	54	Border of hard and soft palate	Right maxilla			7 yr.	Excision		Alive 7 yr.
Roth	11	M	55	Right hard palate	Right maxilla			4 yr.	Resection of right maxilla and palate	Limited resection plus 900–8,000 r with Co^{60} intracavitary applicator and 5,000 r tumor dose with roentgen rays	Alive 10 yr.
Albrecht[1]	12	F	60	Left upper alveolus	Left maxilla, face			6 mo.	Excision and roentgen therapy	Resection of maxillary recurrence and roentgen therapy	Alive 8 yr.
Roth	13	M	63	Right upper alveolus	Hard and soft palate			9 mo.	Resection of right upper alveolus, mucosal stripping of hard and soft palate plus 3,500 r tumor dose with 2 courses of roentgen therapy 3 wk. apart		Alive 16 mo.
Lampe and Zatzkin[13]	14	M	57	Base of tongue	Floor of mouth	Lungs 7 yr., femur cervical lymph nodes		7 yr.	Radium applicator and radon seed implant (no effect), electrocoagulation	Roentgen therapy, 2,600 r in air, using 2 fields	Dead after 14 yr.
Dockerty and Mayo[7]	15	M	35	Base of tongue		Cervical lymph nodes		6 yr.	Radon seed implant into primary lesion and lymph nodes		Alive 6½ yr.

Tinney *et al.*[17]	16	F	61	Upper third of trachea					Radium		Alive 6 mo.
	17	M	50	Upper third of trachea					Radium		Dead after 10 yr. of unrelated disease
	18	F	34	Upper third of trachea					Laryngectomy		Alive 5 yr.
	19	F	32	Upper third of trachea	Peritracheal structures				Roentgen therapy		Alive 5 yr.
	20	M	34	Upper third of trachea	Peritracheal structures				None		Alive 3 yr.
	21	M	35	Middle third of trachea					Diathermy		Alive
	22	M	70	Lower third of trachea					Roentgen therapy and radium		Alive 10 yr.
	23	M	49	Lower third of trachea					Diathermy and roentgen therapy		Alive 3 yr.
Guttman[10]	24	F	32	Trachea	Right main bronchus			2 yr.	Tracheotomy		Alive 3 yr.
Belsey and Valentine[2]	25	F	42	Lower third of trachea	Along trachea		Right pleural implants		Bronchoscopic resection and roentgen therapy	Segmental resection of trachea and plastic reconstruction	Dead after 3 yr.
Roth	26	M	31	Lower half of trachea	Peritracheal structures, tracheoesophageal fistula	Lungs 1 yr., T-10		9 mo.	Bronchoscopic resection	Bronchoscopic resection and roentgen therapy with 4,760 r tumor dose	Alive 13 yr.

mors. We do not feel that we have eradicated the tumor locally, nor have we reached its peripheral extensions. The patient may live with his tumor for ten years. This is not very different from the normal expectation of life at this man's age. The conservative approach that we have undertaken may well prove justified. If the patient were younger and sturdier we would consider more radical surgery, followed by very heavy irradiation, intracavitary or external, or both. It would be a problem to be able to leave enough of the upper alveolus to hold a palate prosthesis.

REVIEW OF THE LITERATURE

There are many case reports of adenoid cystic carcinoma in the oral cavity, paranasal sinuses, and upper respiratory tract, but most of them are inadequate in history or follow-up. Twenty-two cases were selected from the literature that illustrate the character of the tumor. To these 4 were added from our hospital, and the principal features of all 26 cases are set forth in Table I. Eight cases are from the 1945 Mayo Clinic report on diverse tracheal tumors recorded by Tinney *et al.*[17] At that time none of their patients had died of this neoplasm. Two that lived for ten years had been treated by irradiation. In 1953, Clark *et al.*[6] contributed seven more to this series but gave few details. Of the 15 Mayo Clinic cases, 6 were females. Symptoms antedated therapy four to six years. Some lesions were excised or resected. The patients treated by roentgen therapy or radium had tracheotomy or endoscopic diathermy first. Only 5 were still living at the time of the second report; these had been treated surgically. The survival times were not recorded for any of the cases, hence comparison between the two methods of treatment cannot be made.

Table II summarizes the 26 cases according to site of origin.

TABLE II

STATISTICAL SUMMARY OF CASES

Origin of Tumor	Cases	Sex		Age Initial Visit	Duration of Symptoms Before Treatment (Years)	Years Survival after Symptoms. Living Cases		Years Survival, Symptoms to Death Due to Tumor	
		M	F			Cases	Years	Cases	Years
Paranasal sinuses	6	1	5	26–49	¼–5 3 cases	3	1–15	3	½–12
Nose	2	1	1	29–41	1–1¼	1	2	1	5½
Palate and alveolus	5	3	2	47–63	½–7 4 cases	5	¾–10		
Base of tongue	2	2	0	35–57	6–7+	1	6½	1	14
Trachea	11	6	5	31–70	¾–2 2 cases	10*	½–13	1	3
Total	26	13	13	26–70 Av. 42	¼–7+ Av. 3	19	½–15	6	½–14 Av. 8

* One death from other causes after ten years.

TABLE III

RESULTS OF RADIATION THERAPY

Case	Location of Tumor	Initial	Recurrence	Surgery	Radiation Therapy			Result
					Mode	Dose	Time	
1	Left antrum and ethmoids	x		Yes	Roentgen rays hvl. 4.5 mm. Cu	5,061 r	34 da.	Palliation 1 yr.
	Left orbit		x	Yes	Roentgen rays hvl. 1 mm. Cu	1,900 r and 2,000 r in air 2 fields		Palliation
3	Right antrum and mouth		x	No	Radium	2,000 mg. hr.		Palliation
5	Right maxilla and face		x	No	Roentgen rays	3,000 r in air 2 fields		Palliation
6	Right nose, ethmoids and antrum	x		No	Roentgen rays hvl. 6 mm. Cu	5,780 r to tumor	19 da.	Palliation 1 yr.
	Right orbit and base of skull		x	Yes	Co^{60} spherical applicator 6 cm. dia.	9,800 r on surface and 5,500 r at 1 cm.	50 hr.	Neoplasm beyond effective range of applicator
7	Left nose and antrum	x		No	Roentgen rays	6,000 r to tumor		No response
	Left nose and antrum	x		Yes	Radium intracavitary application	3,000 mg. hr.		Followed roentgen therapy Palliation
8	Left posterior naris, nasopharynx, and left antrum	x		No	Roentgen rays	1,000 r		No response
	Left posterior naris, nasopharynx, and left antrum	x		Yes	Radium intracavitary application	5,000 r γ	10 da.	Followed roentgen therapy Palliation
11	Right antral defect		x	Yes	Co^{60} intracavitary application	900–8,000 r in two applications	4 da.	No recurrence after 13 months
					Roentgen rays hvl. 3 mm. Cu	5,000 r to tumor	7 wk.	
13	Hard and soft palate and alveolus	x		Yes	Roentgen rays hvl. 3 mm. Cu	3,500 r to tumor 3 wk. interval 3,500 r to tumor	1 mo. 1 mo.	Too early to evaluate
14	Base of tongue and floor of mouth		x		Roentgen rays hvl. 9 mm. Cu	2,600 r in air 2 fields	30 da.	Palliation
26	Lower ½ of trachea		x		Roentgen rays hvl. 3 mm. Cu	4,760 r to tumor	7 wk.	Palliation

Table III gives the results of radiation therapy for those cases in which the dosage is reported.

Table IV shows the metastases reported in 11 cases, 4 of them with autopsy confirmation.

DISCUSSION

There were as many men as women in this series. The average age at the initial visit was forty-two years (range twenty-six to seventy years). The duration of symptoms before treatment is reported in only 13 cases (2 of these had the tumor in the trachea). It ranged from three months to seven years, the average being three years. One patient died six months after onset of symptoms; 1 is living after fifteen years with the tumor still growing. In the 6 whose deaths are recorded, the average survival was eight years.

Direct extension from the original site

TABLE IV

METASTASES

Case	Living	Dead Autopsy	Dead No Autopsy	Lungs	Pleura	Bones	Lymph Nodes	Heart	Diaphragm	Liver	Spleen	Kidney	Adrenal	Ovary	Uterus	Peritoneum
1	X			L		L	L									
2		X		L	L			D		D				D	D	D
3		X		L	D		D			D	D					
5	X			L												
6		X		L	L			D	D	D		D	D	D		
7			X			L										
8	X			L												
14			X	L		L	L									
15	X						L			L						
25		X			D											
26	X			L		L										
Total Living	5			8	2	4	3			1						
Total Dead		4	2		2		1	2	1	3	1	1	1	2	1	1
Total 11				8	4	4	4	2	1	4	1	1	1	2	1	1

L—Metastases found during life.
D—Additional metastases found on autopsy.

of the tumor was demonstrated in nearly all the cases. The rate of growth of the primary lesion is usually slow. Except for very advanced cases, the neoplasm remains beneath the mucosa. It infiltrates along the perineural lymphatics well beyond the visible and palpable borders of the gross lesion. Infiltrations in advance of the obvious tumor are often missed clinically and by spot biopsies because they may be quite sparse. The location of the tumor frequently makes it difficult to remove it surgically with adequate margins. In none of the cases with an adequate follow-up (this should be at least ten years) has a cure been obtained by any method of therapy.

Even in the face of these dismal results, aggressive action should be taken when this tumor is first seen. Resection should be well beyond the perceptible limits of the tumor, short of destroying vital structures. This should be followed by irradiation, preferably with radium, cobalt or megavoltage roentgen therapy. Softer qualities are inadvisable, since these tumors nearly always occur in the vicinity of bone which is likely to become necrotic from overabsorption of radiation of long wave lengths.[12] The dose necessary to cure is not known. It would seem wise to spread the treatment over a long time, six to ten weeks, so as to bring the total tumor dose above the 6,000 r which appears to have been insufficient.

Reliance should not be placed upon a central source of radium or cobalt unless the cavity is so prepared that any presumed residual neoplasm is within the effective range. Otherwise treatment should be supplemented or replaced by external roentgen therapy.

Metastases generally appear late. They may be asymptomatic in the lungs for years. The only cases that had metastases to local lymph nodes were the 2 in which the primary was in the base of the tongue.

In the later stages of the disease, metastases may appear in the bones, pleura, mediastinum, and abdominal viscera.

SUMMARY

1. Adenoid cystic carcinoma has many synonyms the most common of which is cylindroma. It resembles the cystic type of basal cell carcinoma. It may arise in the major salivary glands or in the mucous and minor salivary glands which are found in the oral cavity, paranasal sinuses, upper respiratory tract and bronchi. Some are reported as arising in the lacrimal glands, skin and breast.

2. The tumor grows slowly, infiltrates insidiously and metastasizes late.

3. Local recurrence is the rule no matter what method of therapy is used.

4. Wide resection and heavy irradiation are advised.

5. Twenty-two cases from the literature are reviewed and 4 personal cases are added to them.

14 Via Cheparro Drive
San Rafael, California

The author expresses his appreciation to Dr. Robert R. Newell for his counsel in the preparation of this paper.

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METASTASIZING GIANT CELL TUMOR*

REPORT OF AN UNUSUAL CASE WITH INDOLENT BONE AND PULMONARY METASTASES

By ELLIOTT C. LASSER, M.D.,† *and* HYMAN TETEWSKY, M.D.
BUFFALO, NEW YORK

WILLIS,[9] in 1949, maintained that no sharp distinction could be made between innocent and malignant giant cell tumors. "The truth is that osteoclastomata, like most other groups of tumors, show a range of structure and behavior; that a few, not initially distinguishable from their benign fellows, invade and metastasize. This malignant behavior does not presuppose any essential change of growth; it is a property, ab initio of certain members of the class." In line with this thought, Lichtenstein,[5] along with Jaffe and Portis, has suggested that giant cell tumors be subclassified into three grades designated numerically as I, II, and III and showing respectively insignificant, moderate, and pronounced atypism of their stromal cells. Lichtenstein, however, in contradistinction to Willis, feels that those giant cell tumors which prove to be aggressive or eventually frankly malignant should be, and are, initially distinguishable from their benign fellows.

The following report of a case would appear to strengthen the conviction that there should be a gradation, rather than a sharp distinction, of the benign and malignant giant cell tumors. It will be shown that in the present instance the histologic structure of the tumor was neither frankly benign, nor frankly malignant, and that the biologic course pursued by this tumor reflects in a large degree its intermediate histologic make-up. As far as can be determined by the authors, this is the first reported instance of a patient with a giant cell tumor, who, in addition to pulmonary metastases, has developed bony metastases that have the classic roentgenographic appearance and clinical behavior of single benign giant cell tumors.

REPORT OF A CASE

C. B., R.P.M.I. No. 66911, was struck by shrapnel on the medial side of the right knee while serving in the United States Army in Italy in September, 1943. He was twenty-nine years old at that time. The skin was not broken, but the knee began to swell so he was hospitalized for ten to twelve days, then returned to duty. After this on several occasions, following trauma to the lower end of the right thigh, there was noticeable swelling in this area and in January, 1944, the patient was sent to the hospital in Naples and then to the Lovell General Hospital. Roentgen examination in March, 1944, showed a destructive bone lesion approximately 6 by 7 cm. in diameter in the distal end of the right femur involving the medial condyle (Fig. 1).

Roentgenograms of the chest at that time were negative. On March 9, 1944, the patient was taken to surgery and prepared for thigh amputation. Frozen sections, however (Fig. 2*A*), proved this to be a giant cell tumor; therefore, amputation was not carried out. The tumor had a well defined capsule beneath the vastus medialis muscle. When this capsule was incised, a large tumor was found which had broken through the bone of the medial condyle of the femur. This was shelled out locally and the area was packed with absolute alcohol.

On section, it was reported that most of the tissue was formed by giant cells together with richly cellular stroma. In general, the giant cells were quite numerous, and in some regions, crowded. The giant cells varied considerably in size and in the number of nuclei. The nuclei were fairly constant in size and in staining qualities. The surrounding cytoplasm had a sharply demarcated periphery. Two types of cells were frequently present in the richly cellu-

* From the Diagnostic X-Ray Department, Roswell Park Memorial Institute, Buffalo, New York.
† At present, Professor, and Chairman of the Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

FIG. 1. Initial roentgenogram showing expanding lesion in supracondylar area of the right femur.

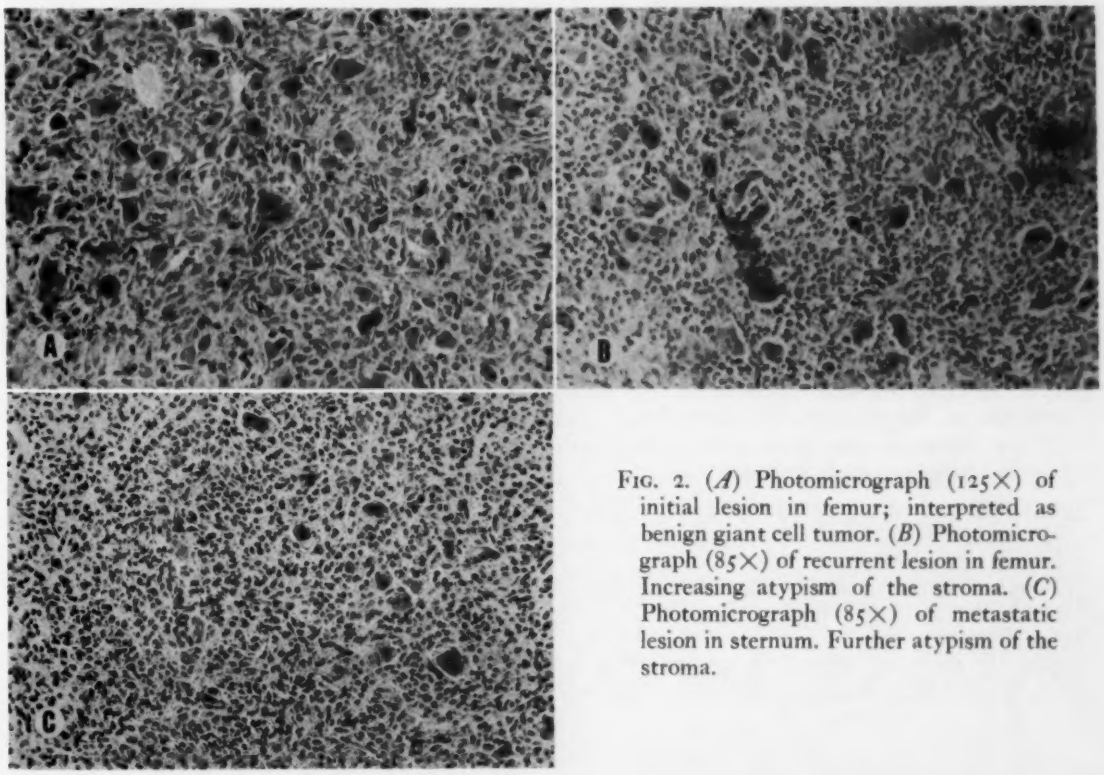

FIG. 2. (*A*) Photomicrograph (125×) of initial lesion in femur; interpreted as benign giant cell tumor. (*B*) Photomicrograph (85×) of recurrent lesion in femur. Increasing atypism of the stroma. (*C*) Photomicrograph (85×) of metastatic lesion in sternum. Further atypism of the stroma.

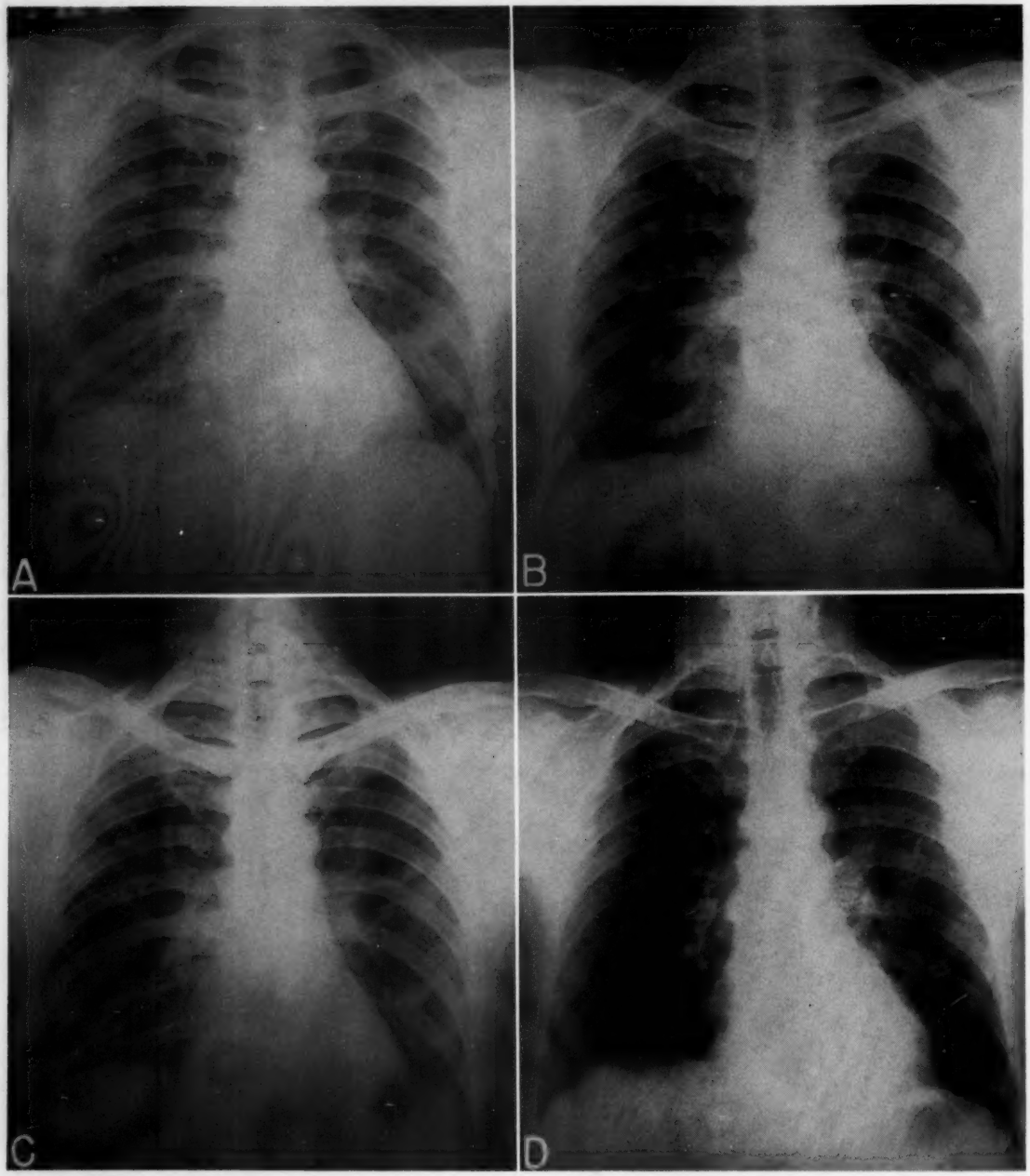

Fig. 3. (*A*) Chest roentgenogram on October 6, 1949. Bilateral pulmonary metastases. (*B*) Chest roentgenogram on February 10, 1950. Progressive pulmonary metastases. (*C*) Chest roentgenogram on March 21, 1951. Spontaneous regression of pulmonary metastases. (*D*) Chest roentgenogram on April 27, 1953. Continued regression of pulmonary metastases.

lar stroma; one, a round cell with a relatively large nucleolus and little cytoplasm which had similar staining characteristics in comparison with cytoplasm of the giant cells. Some mitosis was present in the round cells. The other cell frequently seen in the stroma was fibroblastic with interlacing collagen fibrils. Necrosis was present in sections prepared from the central region of the tumor. In one section from the periphery, a few necrotic bone trabeculae were present beneath the layer of periosteum; however, no atypical bone formation was seen. The report concluded that this was a benign giant cell tumor.

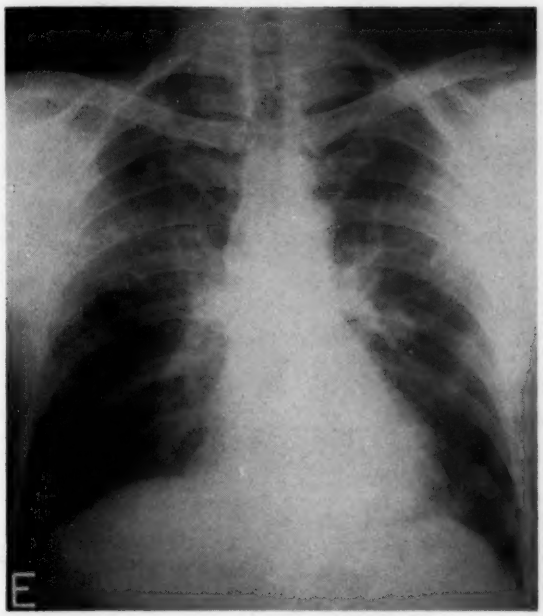

Fig. 3. (*E*) Chest roentgenogram on March 2, 1954. New metastatic lesion in left hilar area.

On May 26, 1944, the patient was transferred to the Walter Reed General Hospital with the right leg in an ischial caliper. He was seen by the Tumor Board at this time and again in July and further observation was recommended. In August, he was once again examined. By this time the tumor had grown larger and had broken through the cortex of the femur, causing some pain and increasing disability. The Board was of the opinion that the tumor had become malignant and suggested that following a biopsy and frozen section immediate midthigh amputation be performed. On September 4, 1944, the patient was again taken to surgery where biopsy and frozen section were carried out. Grossly, the tumor was found to have eroded through a large area in the anterior aspect of the bone just above the knee joint and to have replaced practically all of the epiphysis and metaphysis of the bone in this region. It extended into the suprapatellar pouch and appeared also to have invaded the knee joint through the intercondylar notch. A midthigh amputation was carried out. Sections through the tumor (Fig. 2*B*) revealed the tumor to be made up of rather closely arranged short spindle to irregularly rounded stromal cells with rather pale, finely granular cytoplasm and round to ovoid vesicular nuclei which showed a few mitotic figures. The stromal cells were arranged in no definite pattern; however, there was a decided tendency to form whorls and streams around blood vessels. There were numerous giant cells irregularly distributed throughout the stroma, the cells containing 8 to 30 or more nuclei, which were generally centrally grouped. Here and there were zones of stroma hyalinization with areas of osteoid formation, some of these latter zones being differentiated into imperfectly formed bony trabeculae with some arrangement of cells around these trabeculae simulating osteoblasts. In one section there was a zone showing a marked histiocytic reaction with numerous compact foam cells around which there was no inflammatory response. The tumor generally was extremely vascular with scattered zones of hemorrhage. The conclusion was that this represented a recurrent giant cell tumor. Convalescence was satisfactory. There were no signs of metastases or other involvement of the bone and the chest roentgenogram was negative at this time. He was discharged on December 18, 1944.

The patient was first seen in Roswell Park Memorial Institute on September 12, 1949. His complaint at that time was a pain on the right side of the chest which had appeared suddenly on August 20, 1949, persisting to the date of admission. Roentgenograms of his chest taken at the Wyoming County Community Hospital in Warsaw, New York, on September 2, 1949, showed "a tumor to be present in the right lung." Physical examination at that time was not remarkable. A well healed, midthigh amputation stump was present on the right. No definite therapy was carried out on this visit. A chest roentgenogram on October 6, 1949, showed multiple soft tissue nodules in both lungs (Fig. 3*A*). A roentgenogram of the pelvis dated October 6, 1949, showed no definite abnormalities, although in retrospect, there is early, minimal trabecular destruction in the intertrochanteric area of the right femur and in the subtrochanteric area on the left (Fig. 4*A*).

A chest roentgenogram taken on February 10, 1950, showed definite progression of pulmonary metastases (Fig. 3*B*). Shortly after this, the patient was admitted to the Buffalo Veterans Administration Hospital. The summary of his stay at this institution indicates that on February 15, 1950, he was admitted because of numbness in the left leg ascending progressively to the lower trunk and having

FIG. 4. Roentgenogram of the pelvis on October 6, 1949. Interpreted as negative. In retrospect, there may be early changes in the intertrochanteric areas of the femora. (*B*) Roentgenogram of the pelvis on March 21, 1951. Changes in both femora compatible with giant cell tumors. (*C*) Roentgenogram of the pelvis on August 14, 1954. The lesion in the right femoral stump has been treated by external irradiation. The lesion in the left femur is unchanged since 1951. A new lesion has developed in the symphysis pubis. (*D*) Roentgenogram showing detail of treated lesion in intertrochanteric area of right femoral stump.

commenced about seven days prior to admission. The neurologic impression at that time was that the patient had possible metastatic involvement of the spine at about the D_4 level. Laboratory studies showed a slight increase in acid phosphatase (6.0 King-Armstrong units). No definitive therapy was carried out at this time. He was again seen at the Veterans Administration Hospital in March, 1951, complaining of chest pain and increase in the size of the right stump and a tender area over the mid-anterior sternum with redness and swelling. This sternal mass was biopsied on March 6, 1951. A report of the operative findings at this time indicated that the mass had completely eroded the sternum and extended down into the mediastinum. A considerable amount of this tumor was removed by curettage. Microscopically (Fig. 2*C*), all the sections showed essentially the same picture. The tumor was composed of spindle-formed, small giant cells with a relative sparseness of the classic round cells of benign giant cell tumor of the bone. Further, the giant cells seen in these sections had from a few to several nuclei in contradistinction to the giant cells of the benign type which may have up to 15 or even 100 nuclei in their cytoplasm. Large, sometimes binucleated, cells were found in the stroma with prominent nucleoli. Lastly, mitotic figures of the so-called stromal elements

were present, though not in abundance. The Armed Forces Institute of Pathology reviewed the slides, the history abstract, and the significant roentgenograms at this time and concurred in the diagnosis of a malignant form of giant cell tumor.

The patient returned to Roswell Park Memorial Institute on March 21, 1951. Laboratory findings at that time were as follows: Serum calcium, 10.6 mg. per cent; phosphorus, 6.4 mg. per cent; acid phosphatase, 10.9 King-Armstrong units; alkaline phosphatase, 7.8 King-Armstrong units. Roentgen examination of the pelvis showed a rounded osteolytic lesion situated in the intertrochanteric area of the right femur with widening of the shaft and some thinning and loss of the overlying cortical bone. There were some trabeculae present and the general appearance was compatible with that of an aggressive giant cell tumor. In the intertrochanteric area of the left femur, there was a well demarcated osteolytic lesion crossed by fine bony septa which gave the classic roentgen appearance of a benign giant cell tumor (Fig. 4*B*). Roentgen examination of the chest at this time showed a very surprising but definite regression of the pulmonary metastases (Fig. 3*C*). The patient was complaining of increasing pain in the thigh and roentgen therapy was administered through an anterior right thigh port, the patient receiving 2,160 r to the tumor over a period of twelve days. By July, 1951, the patient had gained eighteen pounds and the pain in the right upper femur had almost completely disappeared. On a return visit on July 30, 1951, however, there was marked tenderness over the lower end of the sternum underneath the scar of the tumor removal, and the patient felt that the area had shown some recent increase in size.

Beginning on August 10, 1951, the patient was treated by deep roentgen therapy over the lower midsternal area, receiving 3,510 r to the tumor region over a period of nineteen days. The therapy was administered over a 10 by 15 cm. port centered over the lower sternum. In October, 1951, and January, 1952, the patient received further courses of roentgen therapy over the right proximal thigh area for recurrent pain. The patient was seen intermittently in this institution between January, 1952, and the last recorded entry of August, 1954. A roentgenogram of the chest obtained on April 27, 1953, showed continued regression of the pulmonary metastases (Fig. 3*D*). A chest roentgenogram on March 2, 1954, showed, however, several new nodules developing in the left chest. The right chest was unchanged (Fig. 3*E*). In July, 1954, the patient had skin tests for histoplasmosis, coccidioidomycosis, and blastomycosis, all of which were negative. Roentgenograms of the pelvis and hips in August, 1954, showed the irradiated lesion in the right femur to be well contained and the lesion in the left femur unchanged. A new lesion had developed in the right pubic bone with expansion of the bone and thinning of the overlying cortex (Fig. 4, *C* and *D*).

DISCUSSION

The case cited is of interest from several standpoints. A giant cell tumor of the lower femur, originally deemed benign and treated by resection of the local tumor, recurred within six months necessitating a midthigh amputation. The patient was than asymptomatic for a period of five years at which time he returned with pulmonary metastases and lesions in the intertrochanteric areas of the femora which had the roentgen characteristics of giant cell tumors. Six and a half years after the original operation a sternal mass was biopsied and was shown to be a giant cell tumor. In comparison with the original sections, this tumor showed somewhat fewer nuclei in the giant cells and some further atypism of the stroma. The pulmonary metastases in this patient have remained indolent and have even shown definite regression in the six year period following their discovery. One of the bone lesions showed signs of aggressiveness and has been effectively controlled by roentgen therapy since 1952. The other one has remained relatively static in appearance for four years now, without any definite therapy directed to this area. Recently, a fourth area of bone involvement has appeared in the right pubic bone.

As far back as 1906, Taylor[8] reported a "giant cell sarcoma" of the lower femur which, eighteen months after the original operation, showed metastatic deposits in the lungs that had the identical histologic characteristics of the primary tumor. It is

not clear from his description, however, whether the tumor he was dealing with was an osteogenic sarcoma showing a few giant cells or was a true giant cell tumor.

In 1931, Dyke[1] published a case of giant cell tumor of the patella in which, five years after the original operation, metastases of the same histologic character developed in the scalp, lung, kidneys, mediastinal and peritoneal lymph nodes. On gross post mortem examination, the patient showed metastases in the ribs and spine, but there were no roentgenograms made and there was no histologic verification of these tumors. The original lesion in this case was treated by curettage but recurred four years later and amputation was carried out, the pulmonary metastases developing six months after this latter operation.

Finch and Gleave[2] have, likewise, recorded a case of giant cell tumor (of the lower femur) of at least nine years' duration, in which metastases to the lungs occurred. The metastases had the histologic characteristics of a primary tumor with numerous typical giant cells and an admixture of fibrosarcomatous tissue. Orr[6] also published a case of giant cell tumor of the lower femur with pulmonary metastases in which the metastatic lesions had the histologic characteristics of giant cell tumor.

More recently, Russell[7] has reported a patient with a primary, apparently benign, giant cell tumor of the tibia who developed pulmonary and subcutaneous metastases four years after treatment of the primary lesion. The subcutaneous metastases were excised and showed large osteoclastic giant cells associated with closely packed round, ovoid, and polygonal mononuclear stromal cells containing nuclei of even shape, size and chromatin content, except where they had become pyknotic and angular. Occasional mitotic figures were present. One of the cases reported by Windeyer and Woodyatt[10] also showed pulmonary metastases in which giant cells of osteoclastic type were found with an irregular cellular stroma. Unfortunately, the primary tumor in their case was resected elsewhere and was reported only as "sarcoma."

The present case is similar to a number of those cited above in that a metastatic process developed after local recurrence following inadequate removal of the primary tumor. This feature has been repeatedly emphasized by other authors.[3,5] The metastases in the present case occurred at a considerable period after treatment of the recurrence, a feature which also may be noted in several of the case reports cited above. The recurrent and the metastatic lesions examined in this patient in many ways reproduced the histologic features of the original lesion but showed, in addition, sufficient stromal abnormalities to justify a histologic diagnosis of low-grade malignancy. Each of the three successive sections showed fewer giant cells with fewer nuclei and increasing atypism of the connective tissue stroma. The fact that several of the osseous metastases have the roentgenographic characteristics of giant cell tumor tends to reflect the histologic similarity of the metastatic lesions with the primary tumor. The extreme indolence of the metastatic bone tumors and the indolence and frank regression of the pulmonary lesions indicate the distinct and unusual lack of aggressiveness of the metastatic deposits. Today, ten years after the onset of the original tumor and five years after the onset of known pulmonary metastases, the patient is alive and well and concerned only with obtaining an adequate prosthesis for the right femoral stump.

Also of considerable interest is the finding of elevated acid phosphatase levels on two occasions. Gomori,[4] who has made an extensive study of the distribution of acid phosphatase in the tissues under normal and abnormal conditions, has noted in a case of giant cell tumor that the giant cells themselves were strongly positive for acid phosphatase while the small spindle cells were negative. It is conceivable that in the

present case the patient was liberating increased amounts of the enzyme into his blood stream from the metastatic lesions.

SUMMARY

1. A giant cell tumor, which apparently was benign originally, developed metastatic lesions five years after right midthigh amputation for local recurrence.

2. The metastatic deposits in this case were unusual in that they (a) produced bony lesions with the roentgenographic appearance and clinical behavior of benign giant cell tumors, (b) produced pulmonary nodulations which have shown extreme indolence and even spontaneous regression.

3. Slightly elevated serum acid phosphatase levels were found on two occasions in this patient and may represent abnormal amounts of the enzyme released from giant cells in the metastatic lesions.

Elliott C. Lasser
Presbyterian Hospital
230 Lothrop Street
Pittsburgh 13, Pennsylvania

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ADDENDUM

Since this article was originally submitted, the patient has developed several other bone metastases which have been treated successfully by roentgen therapy. As of September 4, 1957, the patient remains in generally good health and works actively on his farm.

A CASE REPORT ON THE DEVELOPMENT OF BILIARY TRACT CANCER ELEVEN YEARS AFTER THE INJECTION OF THOROTRAST*

By SHIGEO OKINAKA, M.D., KIKU NAKAO, M.D., HIROSHI IBAYASHI, M.D., (*Prof. Okinaka's Clinic, Department of Medicine*); MASANORI NAKAIDZUMI, M.D., HIROTAKE KAKEHI, M.D.,† *and* TAKASHI SUGIMURA, M.D.‡

TOKYO, JAPAN

THOROTRAST is a 25 per cent colloidal suspension of thorium dioxide (ThO_2) with 3–10 mμ size particles. Some thirty years have elapsed since it was first applied clinically as an opaque medium for the visualization of liver and spleen (Oka,[15] 1929). Over that time many studies have been made and have proved its value, but there still remain some unsolved problems having to do chiefly with its late side effects. At present, the appearance of late effects is presumed to be related to the following: (1) After intravenous injection of ThO_2, this substance is deposited in various organs of the reticuloendothelial system, especially liver, spleen and bone marrow, and is not soluble in body fluids. Therefore, very little of it is excreted from the body and it is stored in the tissues for a long time as a foreign substance; (2) thorium is radioactive (half life 1.8×10^{10} years) and emits α-rays of highly ionizing energy, causing injurious effects on the surrounding tissues.

Because of these two considerations, the usefulness of thorotrast as an opacifying agent has remained controversial. Fibrosis of depositary tissues and development of malignant tumors as delayed effects after its use have been encountered.

There are many reports on tissue fibrosis, but those concerning the development of malignant tumors are scarce. We have observed a female patient who received an injection of thorotrast intravenously and died eleven years later with the development of carcinoma of the biliary tract. At autopsy the pertinent organs were subjected to chemical analysis and the deposition of thorium was also studied by autoradiography.

REPORT OF A CASE

Patient M.I., a Japanese female, died at the age of forty. The clinical diagnosis was cirrhosis and cancer of the liver.

Family History: It was found that her mother died of liver cancer when she was sixty-eight years old.

History of the Present Disease: In 1940, the patient was admitted to another hospital because of anemia, splenomegaly and distention of the abdomen. She stayed in the hospital for about one month and recovered after having received treatment with iron compounds. In retrospect, it appears probable that thorotrast examination was made at that time. Since then, she had been healthy until 1948, when delivery of a child was accompanied by a large amount of bleeding. This was followed by lassitude and anemia. From the middle of December, 1950, her abdomen had become gradually distended; at the same time the abdominal wall became markedly rigid. Slight dilatation of the veins of the upper and lateral regions of the abdomen was noted. On January 1, 1951, she was diagnosed as having cirrhosis of the liver. By the end of February, ascitic fluid had been removed by puncture on five occasions at intervals of ten or fifteen days, and the amount of the total fluid removed approached six liters. Around that time jaundice had begun to appear insidiously. The patient lost her appetite, complained of pain in the upper region of the abdomen and became very weak. She was hospitalized in Dr. Okinaka's Clinic on February 26, 1951.

* From Faculty of Medicine, University of Tokyo, Department of Radiology, Director: Dr. Nakaidzumi.
† Department of Radiology, Chiba Medical College, Chiba.
‡ Cancer Institute, Japanese Foundation for Cancer Research, Tokyo.

Physical Findings: Physical build was normal. There was marked jaundice. Vascular dilatations were present on the chest, back, both upper extremities and hands. The heart was somewhat enlarged to the right. In the lungs, middle grade rales were heard in the right middle and lower regions. The abdomen was tympanitic and distended to a high degree (circumference of the abdomen 91.5 cm.). After removal of 4.5 liters of ascitic fluid, the liver was felt 3 cm. below the right costal margin and was hard. The spleen was felt about 6 cm. below the left costal margin and was likewise hard. Edema of the lower extremities was noted.

Laboratory Findings: Urine: The urine was cloudy and showed positive albumin. Bilirubin and urobilinogen were present in significant quantities. The diazo-reaction was also positive. Many white blood cells were found in the sediment of the urine. Stool: The stool was of normal color but showed a positive reaction to occult blood by guaiac test. A few Ascaris eggs were found in it. Blood: The hemoglobin value was 76 per cent by Sahli's method, the erythrocyte count was 3.05 million, the color index 1.23 and the reticulocyte count 1.5 per cent. The white blood cell count was 7,200 and the platelet count was reduced to 30,500. The differential count showed a slight shift to the left of the neutrophils with 7.0 per cent band forms, 71.0 per cent segmented neutrophils, 2.5 per cent esoinophils, 0 per cent basophils, 6.0 per cent monocytes, 13.0 per cent lymphocytes and 1.5 per cent plasma cells. The erythrocytes showed slight irregularities and deformities, and polychromatophilia was noted. Bleeding time was 23.5 minutes and the tourniquet test was positive. The Wassermann test was negative. Total serum proteins were 5.08 gm. per cent, with 18.1 per cent albumin, 4.8 per cent α-globulin, 8.2 per cent β-globulin and 68.9 per cent γ-globulin by method of electrophoresis. There were no abnormalities in the esophagus on fluoroscopic examination. The ascitic fluid was slightly hemorrhagic but contained no malignant tumor cells. Liver function test: The serum bilirubin was sixty Meulengracht units, and the direct diazo-reaction for bile pigment was positive. The bromsulphalein test showed 25 per cent retention in thirty minutes. Takata's reaction was positive and Kunkel's test was 23.6 units. Nonprotein nitrogen was 58 mg. per 100 ml. of serum.

Hospital Course: The patient expired on March 9, 1951, eleven days after admission to the hospital.

Pertinent Autopsy Findings: Liver: The liver weighed 1,400 gm. and the surface was hard and irregular with very conspicuous yellow pigmentation. On cut surface there were multiple, soft, yellowish, egg-size or thumb-size nodes scattered throughout. The gallbladder was edematous and empty. No abnormalities were found in the extrahepatic ducts or the portal veins. Spleen: The spleen weighed 440 gm. and was hard. The amount of blood contained was normal. Quite a number of fibrotic areas were seen, and abnormal, light-yellowish deposits were dispersed among them. Bone marrow: The bone marrow of the upper two thirds of the femora was red, and contained yellowish nodes.

Microscopic Findings: Liver: The main finding was carcinoma of the common duct. The liver cells were irregularly shrunken, and vacuoles and edema were conspicuous. Carcinomatous infiltration was noted between the liver cells. Fibrotic change in the portal region was marked, and deposition of foreign substance was heavy in this area. The greatest amount of the deposited substance was found within the cells proper. Rebuilding of the biliary ducts and portal stenosis were noted as were marked arterial distention and fibrosis. Spleen: Marked hyaline changes were present and there was considerable fibrosis around the hyaline areas and their arteries. The follicles were atrophic or had disappeared altogether. Fibrillo-fibrosis of the red pulp was seen. Diffuse bleeding, vacuole formation, nuclear pyknosis of reticulum cells and deposition of hemosiderin were also noted. Heavy deposits of foreign substances in the trabeculae and around the arteries, and small amounts in the follices were observed. An increase in the number of plasma cells was found near the foreign substance deposits. Bone marrow: Foreign substance deposits were observed in the endoreticulum, surrounded by plasma cell infiltration. Parenchyma cells were relatively normally maintained. Sparsely scattered carcinoma metastases were seen.

Deposits of Foreign Substances in the Tissues: Both liver and spleen, after being fixed in formalin, were prepared in sections about 1.5 cm. thick. Roentgenograms of these tissue-sections revealed unusual shadows as shown in Figures 1 and 2. Then, by the mounting and stripping methods the sections were cut to 5

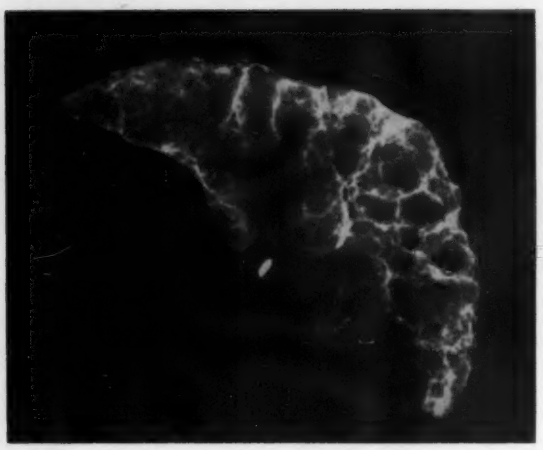


Fig. 1. Roentgenogram of the liver section 1.5 cm. in thickness. White part shows thorotrast deposition (½).

mμ in thickness and autoradiographed (Fig. 3 and 4). Figure 3 shows in the center a star-like cell with α-ray tracks. In Figure 4, many α-ray tracks from the connective tissues of the periportal region can be seen. Fibrotic changes in this region were very remarkable. In the spleen, α-ray tracks were also noted in the connective tissues.

Each section of the formalin fixed liver and spleen was ashed. The weight of ashes was 0.97 per cent and 2.41 per cent of the initial liver and spleen specimens, respectively. One part of the ashes was dissolved in hydrochloric acid and then evaporated to dryness twice. (1) The dried material was extracted with hydrochloric acid and was filtered. The remainder was called Precipitate 1. (2) Sulfureted hydrogen gas was bubbled through the filtrate and then the liquid was filtered. The remainder was called Precipitate 2. (3). The second filtrate was boiled, adding concentrated nitric acid in order to oxidize, and then its hydroxide was precipitated by alkalinization upon the addition of liquid ammonia and was filtered. The remainder was named Precipitate 3. (4) Sulfureted ammonium was added to the third filtrate, the precipitate was filtered off, and named Precipitate 4. (5) Ammonium oxalate was added to the fourth filtrate and its precipitate was called Precipitate 5. (6) Ammonium phosphate was added to the fifth filtrate and the precipitate was named Precipitate 6. Then, the radioactivity of each precipitate was measured using both Lauritsen's electroscope and a Geiger-Müller counter. The results are shown in Tables I and II.

A portion of the ash from the spleen was used to measure its radioactivity in order to draw a decay curve of radiation. Since this curve coincided with the disintegration curve of thorium emanation (Tn) (Fig. 5), we were able to deduce that it was thorium emanation. We could also explain that the difference between the values of the radioactivity of Precipitates 2 of the liver and spleen was due to the decay of thorium emanation between

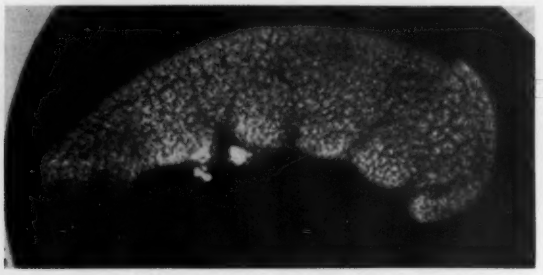


Fig. 2. Roentgenogram of the spleen section 1.5 cm. in thickness. White part shows thorotrast deposition (½).

Fig. 3. Alpha-ray tracks from a star-like cell in the center of the liver section.

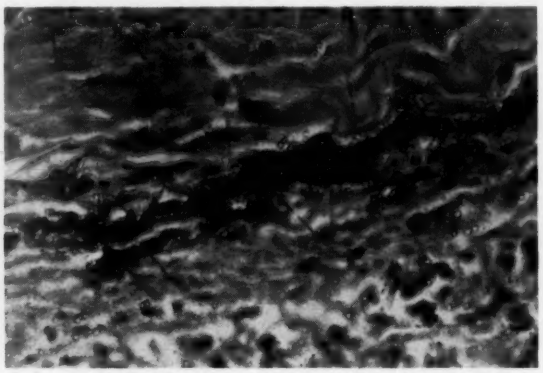


Fig. 4. Many alpha-ray tracks from connective tissue in portal region of the liver section.

Table I

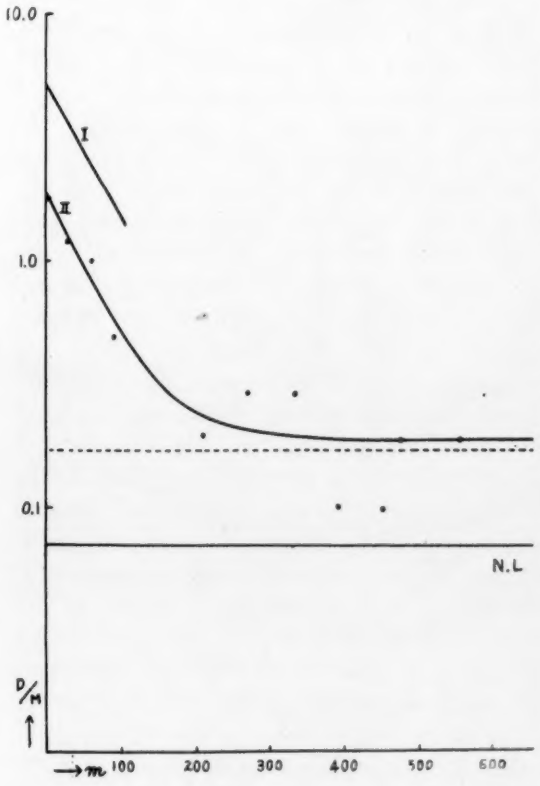
RADIOACTIVITY OF EACH PRECIPITATE FROM LIVER

Precipitate	Liver	Date	Natural Leak	Lauritsen's Electroscope	Geiger-Müller Counter
	Per Cent		D/M	D/M	C/M
1	79.41	Nov. 2, 1952	0.13	124.35	956.64
2	0.74	Nov. 2, 1952	0.13	0.57	4.38
3	8.25	Nov. 2, 1952	0.13	28.94	222.62
4	0.90	Nov. 2, 1952	0.13	0.21	1.61
5	1.84	Nov. 2, 1952	0.13	0.00	0.00
6	2.14	Nov. 2, 1952	0.13	0.00	0.00

Table II

RADIOACTIVITY OF EACH PRECIPITATE FROM SPLEEN

Precipitate	Spleen	Date	Natural Leak	Lauritsen's Electroscope	Geiger-Müller Counter
	Per Cent		D/M	D/M	C/M
1	42.18	Jan. 24, 1952	0.14	185.05	1321.80
2	28.21	Jan. 24, 1952	0.14	74.49	532.08
3	23.12	Jan. 24, 1952	0.14	70.58	504.14
4	1.05	Jan. 25, 1952	0.15	0.06	0.40
5	1.82	Jan. 25, 1952	0.15	0.07	0.47
6	1.17	Jan. 25, 1952	0.15	0.05	0.33



the dates when the measurements were made. Moreover, another portion of the ash from the liver was dissolved in $KHSO_4$, and then extracted with dilute sulfuric acid. Ammonium chlorate was added to the extracted solution and the thorium was precipitated together with other metals of the third group and oxidized after being burnt in a crucible. A given amount of this oxidized material was used to measure its α-radiation activity employing Lauritsen's electroscope, and the activity was compared with that of a standard sample, which had been prepared to contain both 80 mg. of ferric oxide and 11 mg. of thorium dioxide. The α-radiation activity of this standard sample was 12.56 D/M.

The amounts of thorium dioxide deposited in the liver and spleen, respectively, were deter-

Fig. 5. Comparison of the decay curve of the radioactive substance in the spleen with the disintegration curve of thorium emanation (Tn). I. Theoretical decay curve of Tn. II. Decay curve of the radioactivity in the spleen. Dotted line shows the radioactivity passing through the aluminum cover of the Lauritsen electroscope. Unbroken line shows the natural leakage.

mined as follows: Liver: 93 mg. of oxidized substances was obtained out of 310 mg. of liver ash. The radioactivity of 91 mg. of oxidized substances was 84.42 D/M. From these data, the amount of thorium dioxide deposited in the liver was estimated as 0.25 mg. per 100 gm. of liver. Spleen: In the same way, 249 mg. of oxidized substances was obtained out of 356 mg. of spleen ash, and the radioactivity of 91 mg. was 76.76 D/M. Therefore, the amount of thorium dioxide deposited in the spleen was estimated as 1.3 gm. per 100 gm.

DISCUSSION

This patient had been admitted to another hospital with suspected Banti's disease eleven years previously. It was learned that in that hospital, thorotrast was used widely as an opaque medium for the visualization of liver and spleen in various diseases, so it is presumed that this patient, too, was subjected to the usual procedure. Unfortunately, the patient's hospital chart is not available because of fire loss due to air-raids during World War II. The only means of gathering data about the patient was to ask a physician who worked in the hospital at that time, and it was learned from him that the patient might have been injected with 75 ml. of thorotrast.

Hourly Alteration of Deposited Thorotrast in Tissues: It has been reported that immediately after injection from 50 per cent (Taft[21]) to 60–70 per cent (Adachi[2]) of thorotrast is deposited in the liver and 10 per cent (Adachi, Taft) in the spleen; or 60–70 per cent (Popper and Klein[17]) in the liver and spleen combined. Jacobson and Rosenbaum,[8] after injecting 75 ml. of thorotrast, found a 27 per cent residue in the liver five years later. Seventeen years and eight months after injecting 36.4 gm. of thorotrast over a period of eight days, Shimanouchi and others[20] found 11.3 per cent and 1.35 per cent of the injected material in the liver and spleen, respectively. In our case, if 75 ml. of thorotrast were really injected intravenously (ThO_2 18.75 gm.), after eleven years the deposition in the liver was 18.7 per cent, in the spleen 25.8 per cent. Therefore, the residue in both organs was still marked. However, if the distribution to the organs after injection is as the data from the literature indicate, we must consider the possibility that a small quantity has gradually been excreted. In one case, compared with Shimanouchi's case, the percentage of the deposited thorotrast in the spleen is much higher, but this fact is understandable, since the mode of distribution to various tissues could be altered by the different diseases of the liver and spleen present at the time when the thorotrast is injected. In connection with this, the redistribution in the tissues must also be taken into consideration, and it is likely that the amount of deposited thorotrast in the various parts of these tissues selected as specimens might be different.

Side Effects, Especially Late Effects: Pohle and Ritchie[16] and others[4,6,7,24] found through animal experiments that fibrosis occurs where thorotrast is deposited. This fact was also observed clinically.[8,20,23] The fibrosis is caused not only by the foreign substance deposition, but also by the long radiation effect. In our case, as in Shimanouchi's case, the histologic picture of liver cirrhosis is unusual, fibrosis being more marked where the deposition is more heavy. As regards the relationship between the development of carcinoma of the common duct and the deposition of the foreign substances in the liver, there are some cases reported in Japan,[14,22,26] in which Schistosomiasis Japonica and liver dystoma were thought to have caused cancer, but these instances are generally believed to be rare. On the other hand, the development of cancer of the liver in hemochromatosis is well known.[5,25] Thorotrast emits strongly ionizing α-rays which irradiate for a long time and destroy the surrounding tissues. In animal experiments it has already been proved that thorotrast is a cancerogenic agent, as are mesothorium (disintegration) and fission products of plutonium (Sr^{89}).[10] However, there are only a few cases of cancer reported as being caused from using thorotrast clinically. Recently, Thomas, Henry and Kaplan[32] reported 5 cases based on review of the

literature; namely, 1 case of endothelial sarcoma and 2 cases of liver tumor (McMahon, Murphy and Bates[12]), 1 case of lymphoid leukemia (Squire) and 1 case of sarcoma of the kidney observed nine years after the use of thorotrast for pyelography (Zollinger[27]). In addition to these cases, another new case of lung cancer is reported by Abrahamson, *et al.*[1] It would thus seem to appear that the percentage of incidence of cancer from the use of thorotrast is very low. Bauer[4] and Selbie[19] emphasize, that thorotrast as a causative agent for human cancer cannot be eliminated until one investigates the associated conditions, such as the precise thorotrast dosage used, hereditary predisposition of the individual and careful observation for a sufficient length of time. In our case, we were not able to determine the real cause of the carcinoma, nor were we able to find any definite morphologic alterations of the tumor cells around the region where thorium was deposited, although an etiologic relationship between the long irradiation and the development of carcinoma could not be ruled out.

SUMMARY

1. The clinical and autopsy findings of a female patient who died of carcinoma of the common duct eleven years after having received an injection of thorotrast were reported.

2. The liver and spleen were examined with special care histologically, and at the site of thorotrast deposition α-ray tracks were identified. The percentage of thorium residue was measured by chemical and radiologic means.

3. No direct relationship was found between the long thorium irradiation and the causation of the cancer, but some etiologic dependence could not be ruled out.

Kiku Nakao, M.D.
Department of Medicine
University of Tokyo
Tokyo, Japan

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EFFECTS OF RADIATION QUALITY, TARGET-AXIS DISTANCE, AND FIELD SIZE ON DOSE DISTRIBUTION IN ROTATION THERAPY*

By EDITH H. QUIMBY, Sc.D., *and* BEVERLY S. COHEN, B.A.
NEW YORK, NEW YORK

IN RADIATION therapy of localized malignant disease, the object of treatment is to deliver an adequate dose to the cancer, while doses to normal tissues are maintained at levels low enough to avoid permanent damage. For the deep-seated, circumscribed lesion, rotation therapy is frequently the method of choice. This is cross-fire technique raised to the limit, with the largest possible number of ports. With proper selection of physical factors, the tumor-bearing region can generally be given a uniform dose which is considerably higher than that to any other tissues.

The tumor is usually placed at, or close to, the axis of rotation, and the efficiency of the therapy may be described by the ratio between maximum skin dose and axis dose. In general, the smaller this ratio, the more satisfactory is the arrangement.

Two sets of factors influence this ratio. One group may be called *intrinsic;* it comprises the size and shape of the body section, the size of the tumor mass, and the nature of the tissues traversed, such as muscle, bone or lung. These factors cannot be modified by the radiologist; they are characteristic of the individual patient. The others, which may be called *extrinsic,* are the radiation quality, target-axis distance, and (to a certain extent) field size. Within limits these may be modified in the treatment of a particular case.

It is the purpose of this study to investigate the effect of variation of these extrinsic factors on the efficiency of rotation therapy, for various positions in three regions of the body—head, pelvis, and thorax. So far as is known, there has been no comprehensive effort of this sort. A search of the literature reveals a number of studies over quite limited ranges of quality and phantom size. Many of these were done with cylindrical phantoms, some of which were of considerably less than unit density. The statement is sometimes made that for all practical purposes data from clyindrical phantoms can be used for any anatomic shape which is nearly elliptical, provided the area of the cylinder is the same as that of the ellipse. This is an over simplification of the problem. Obviously, only doses to the centers of the circle and the ellipse could be the same; for points away from the center, and especially for those near the skin, differences might be considerable. Moreover, the flatness or elongation of the ellipse, and the quality of the radiation are factors which influence the relation. In Figure 1 are presented curves giving the ratio of an axis dose in an elliptical phantom to that in a cylindrical one, for three ellipses having the same area, and for a wide range of radiation qualities. Values are the average of those for 25, 50, and 100 sq. cm. fields; for any particular phantom and radiation quality these did not differ by more than 3 per cent among themselves. (These data were calculated according to the method used throughout the present paper.) For radiation of half value 4.0 mm. or more of copper, or for ellipses of which the longer axis is not more than one and one-half times the shorter, doses at the center vary less than 10 per cent from those at the center of the cylinder of equal area. Beyond these limits of shape and quality, doses in the elliptical mass become consider-

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From the Department of Radiology, College of Physicians and Surgeons, New York, New York.

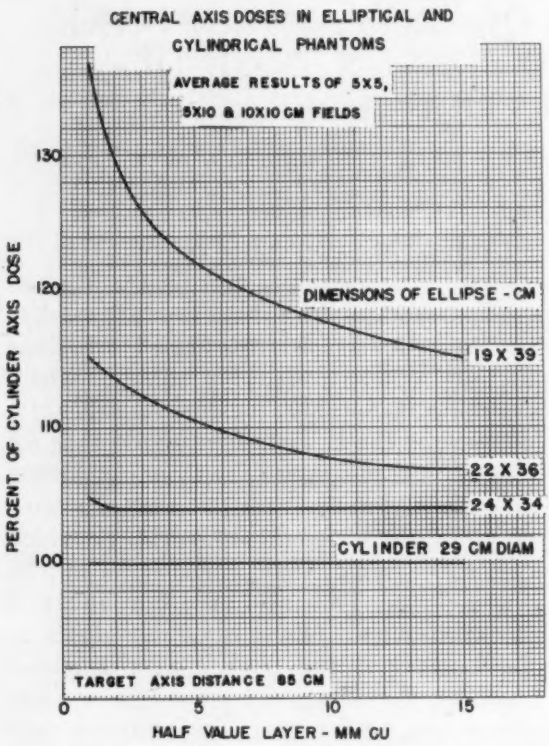

FIG. 1. Curves showing relation between axis doses in elliptical and cylindrical phantoms. Dose in elliptical as percentage of dose in cylindrical phantoms, for each phantom shape and radiation quality.

ably higher than those in the cylinder. Doses in elliptical sections and those in body contour sections of the same transverse and anteroposterior diameters were found to be in good agreement.

CALCULATED DOSAGE DATA

In general, doses for the present study were not measured but were calculated according to a method recently published by our group.[2] Some were, however, checked by ionization measurements in a rotating pressdwood phantom. The range of radiation qualities considered was from half value layer 1.0 mm. of copper to 15.0 mm. of copper; this last corresponds to the radiation from cobalt 60. A target-axis distance of about 85 cm., corresponding to a target-skin distance of 70 or 75 cm. is suitable for rotation therapy in most instances. Accordingly, this was used in all basic calculations. In some cases it would be advantageous to use a shorter target-axis distance; 65 cm. is about the shortest practicable, and a considerable number of calculations were done with this factor. Longer distances are not usually employed except for radiation in the supervoltage range; a few studies for the higher half value layers were made at target-axis distance of 115 cm.

In order to decide on cross-section areas and field sizes to be used in this study, we reviewed the rotation therapy records of the Presbyterian Hospital. In Table 1 are shown maximum, minimum, and average dimensions of patient cross-sections, and maximum and minimum field sizes for three regions.

Basic data for each region were obtained for the average individual. Each cross-section was drawn to scale from anatomic charts. In the head, calculations were made for different field sizes with the axis placed at a central point, and at points 3.0 cm. posterior to the center, and 2.0 cm. lateral. In the pelvis, points were chosen to correspond to cervix, bladder, and parametrium; in the thorax, to esophagus and lung (See Fig. 3–9).

TABLE I

DIMENSIONS OF PATIENT CROSS-SECTIONS, AND OF FIELD SIZES

Anatomic Region	Maximum Dimensions	Minimum Dimensions	Average Dimensions	Maximum Field	Minimum Field
	cm.	cm.	cm.	cm.	cm.
Head	24×17	17.5×14	20×15.5	6× 7	4×4
Pelvis	37×31	30 ×18	34×24	12×15	9×9
Thorax (arms up)	44×24	26 ×17	30×22	12×17	6×6

For each section, a reasonable range of field sizes was used, covering those which had been found to be employed in practice. All fields were square. The axis depth doses in fields of a particular area do not vary much for circular, square, or slightly elongated shapes. However, in rotation therapy the skin dose is strongly dependent on the transverse dimension of the field, since this determines the length of time the skin point remains in the beam. Even though elongated fields are frequently used in rotation therapy, our discussion can reasonably be based on square ones. Field size is specified as the *average* area on the skin. For a given patient it will be a little larger for the region closest to the axis of rotation, and a little smaller for that far-

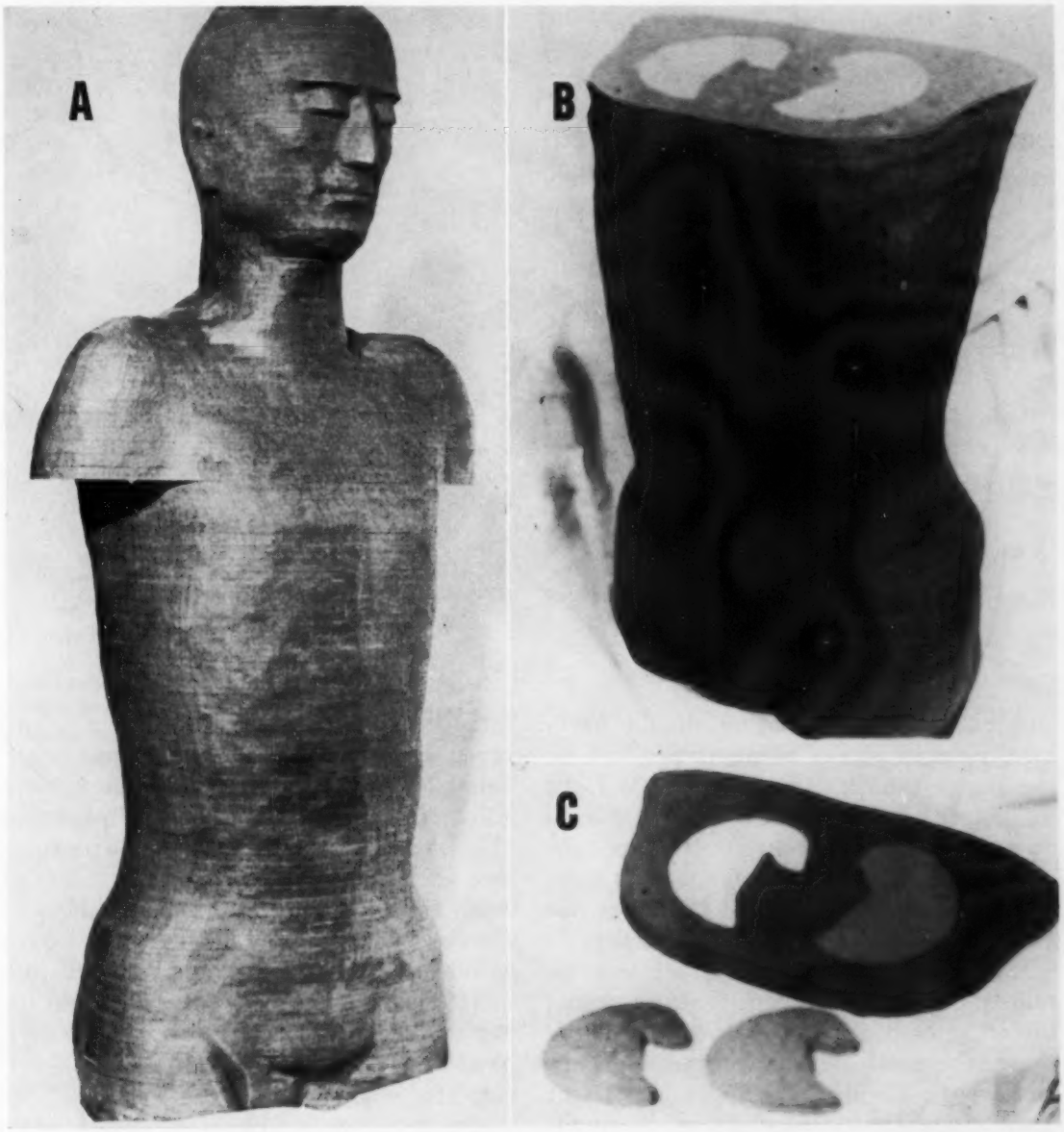

Fig. 2. (*A*, *B* and *C*) Pressdwood phantom man, with lung sections of cork of density 0.3. Cork sections can be removed and unit density material substituted for comparative measurements. Small ionization chambers can be inserted at various points within the phantom.

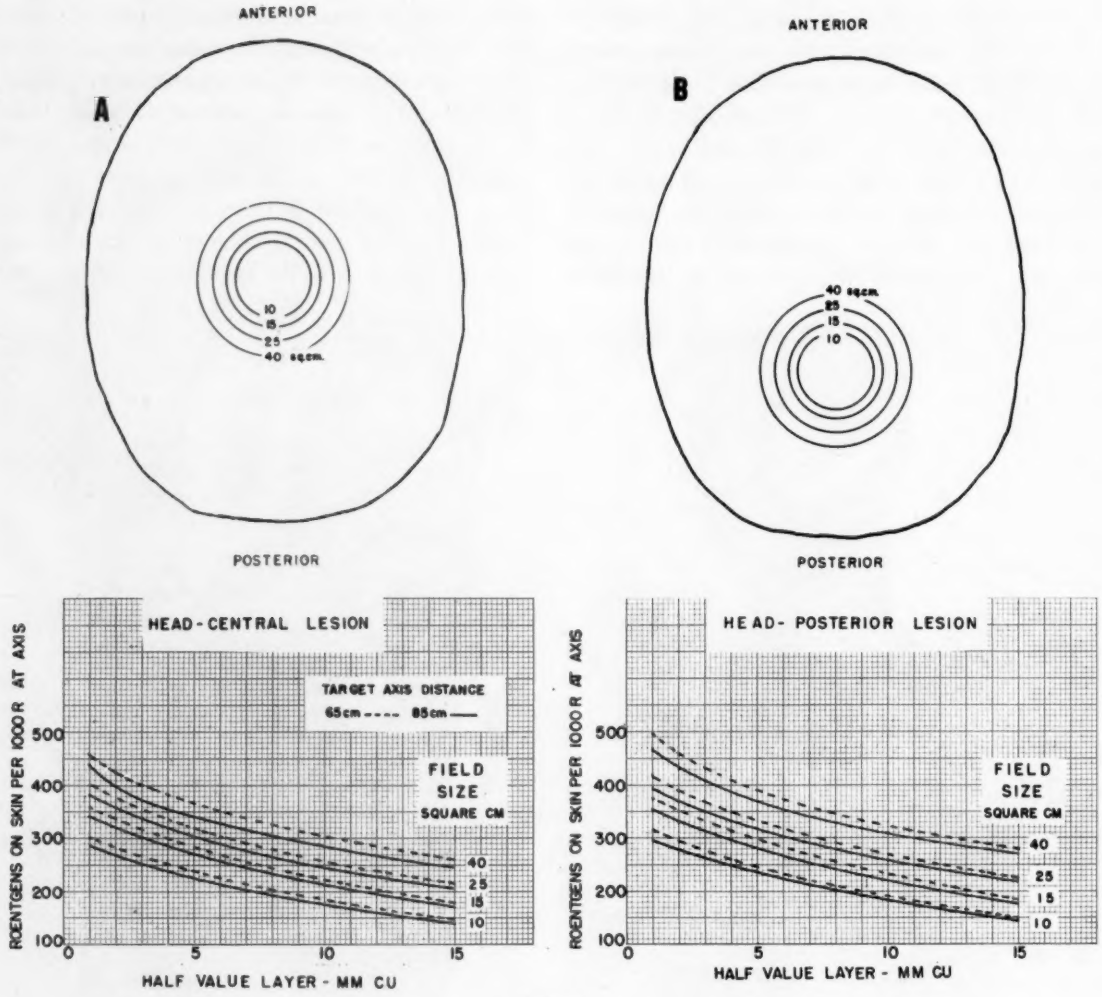

FIG. 3.

thest away. The variation should never be more than plus or minus 10 per cent for the shortest target-axis distance, and less for longer ones. The variations in partial dose contributions tend to counteract each other, and the net result cannot be in error by as much as 4 per cent. This does not affect comparisons to be presented here.

In the head and pelvis, tissue was assumed to be of unit density throughout; the effect of bones was discounted. In the chest, the small density of the lungs increases the depth dose appreciably, but little quantitative information is available as to the necessary correction factors. Jacobson and Knauer[4] constructed a phantom in the shape of the human body, with lung sections of cork, of density 0.3, and made many measurements in stationary fields, and a few with rotation with a cobalt 60 unit. We copied their phantom (Fig. 2) and made measurements with rotation at various qualities, using an array of small Sievert-type ionization chambers to obtain dose distribution. The actual data will be published elsewhere. The factors indicate increases of between 20 and 40 per cent over values for the unit density phantom. Our doses for the thorax are corrected on this basis.

LESIONS IN HEAD

The results for lesions in the average head are shown in Figures 3 and 4. In

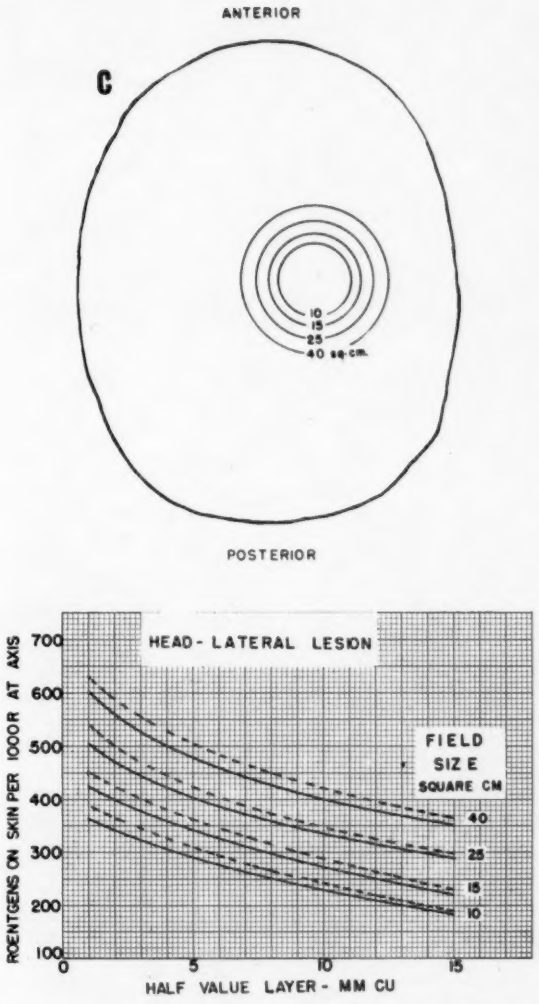

Fig. 3. Curves showing maximum skin dose per 1,000 r at axis, for head lesions, for various fields, distances, and radiation qualities. In all cases the dotted curves are for target-axis distance 65 cm., and the solid ones for 85 cm. (*A*) Central lesion. (*B*) Lesion 3 cm. posterior to center. (*C*) Lesion 2 cm. lateral to center.

Figure 3 are shown maximum skin doses for 1,000 r delivered at the axis of rotation, for different fields and radiation qualities, and for two target-axis distances. The three positions of the axis of rotation are indicated in the three parts of the figure, together with the area covered by each field. The position of maximum skin dose is always at the skin point nearest to the axis.

From these curves it appears that even with the largest field customarily employed, and using a relatively poor radiation quality and short target-axis distance, the skin never receives as much as two-thirds of the axis dose. Such a ratio is generally accepted as practicable for rotation therapy. The relation, of course, improves with the increased distance and increased half value layer, but the change is rather slow. With radiation of half value layer 3.0 mm. of copper and 85 cm. target axis distance, using the largest field, the skin receives only about half the axis dose, for any near-central position. For smaller fields the situation is even more favorable.

In Figure 4, the data for the central lesion have been replotted to show more explicitly the effect of variation in field size. On the basis of the data presented in these two sets of curves, it may be calculated that, for lesions situated anywhere in the interior of the average head, rotation therapy should be a good technique, even if the only roentgen equipment available is a 200 kv. machine of moderate output. Since variations in head size and shape are relatively small, this conclusion may be generalized for all heads.

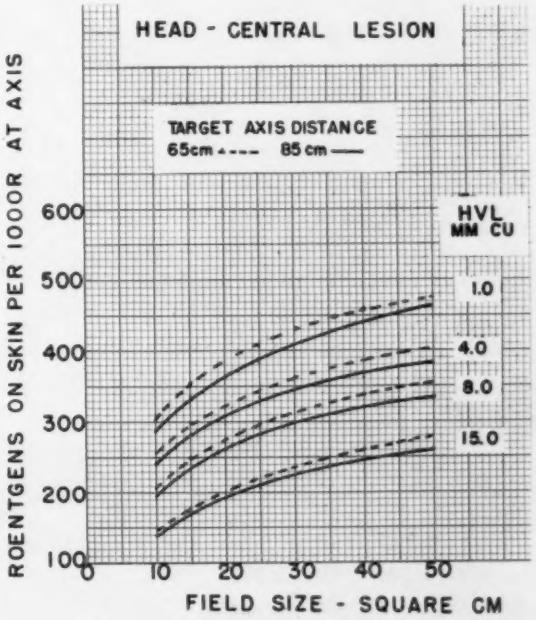

Fig. 4. Curves showing change in skin dose with field size for central head lesion for 1,000 r at axis in all cases.

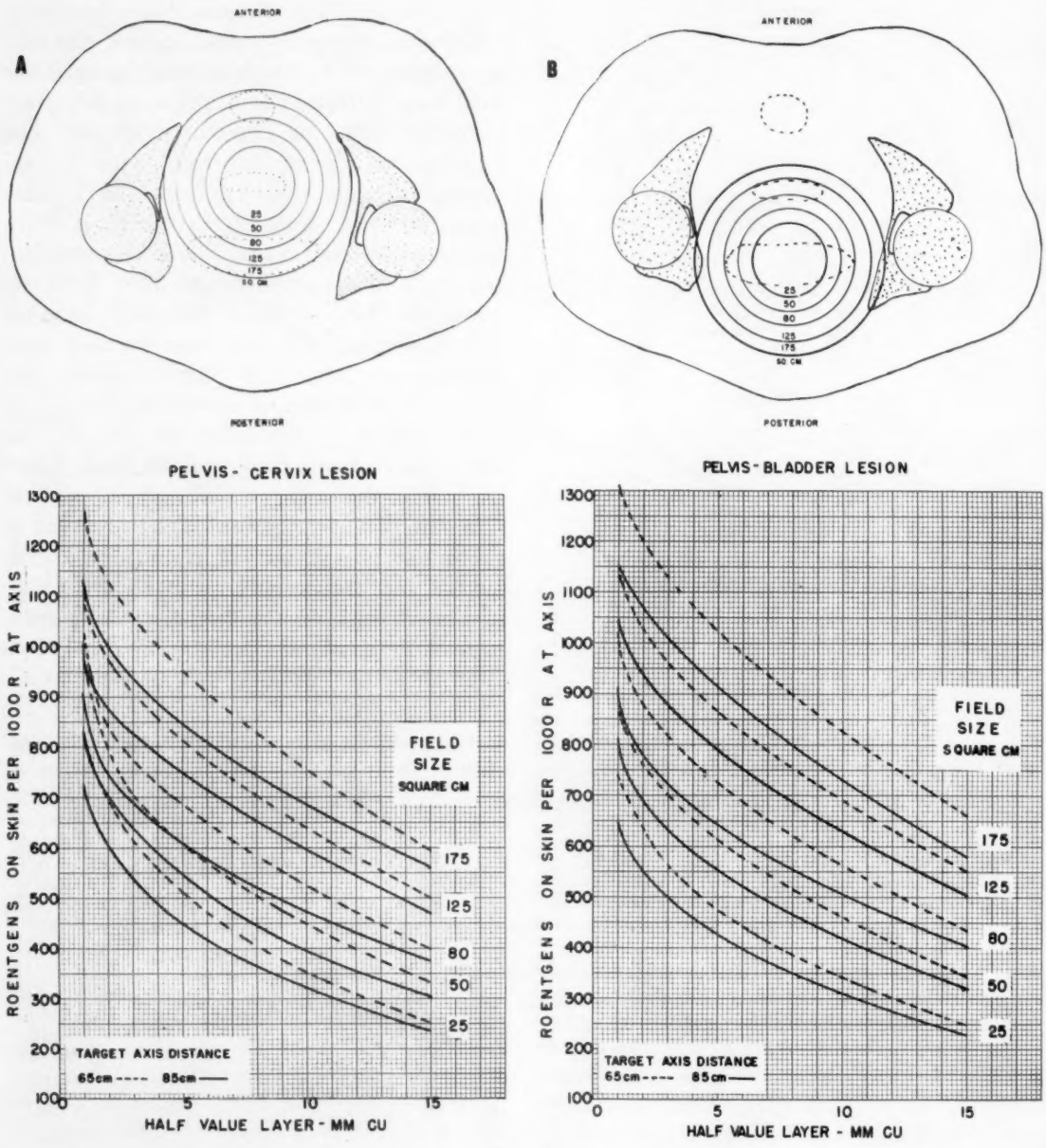

FIG. 5.

LESIONS IN PELVIS

Data for the average pelvis are shown in Figure 5, the curves being plotted in the same manner as those of Figure 3. The three positions of the axis of rotation represent the cervix, the bladder, and the parametrium. In Figure 6, some of the data are replotted to show the effect of field size, for the cervix position and the 85 cm. distance. The effect of change in target-axis distance is detailed in Figure 7. Figure 8 gives some data for central lesions in larger and smaller anatomic cross-sections.

From data of Figures 5 and 6 it is seen that for any lesion in the interior of the average pelvis, rotation therapy is not practicable with roentgen rays of half value layer 1.0 mm. of copper and a target-axis distance of 65 cm. With these factors and a

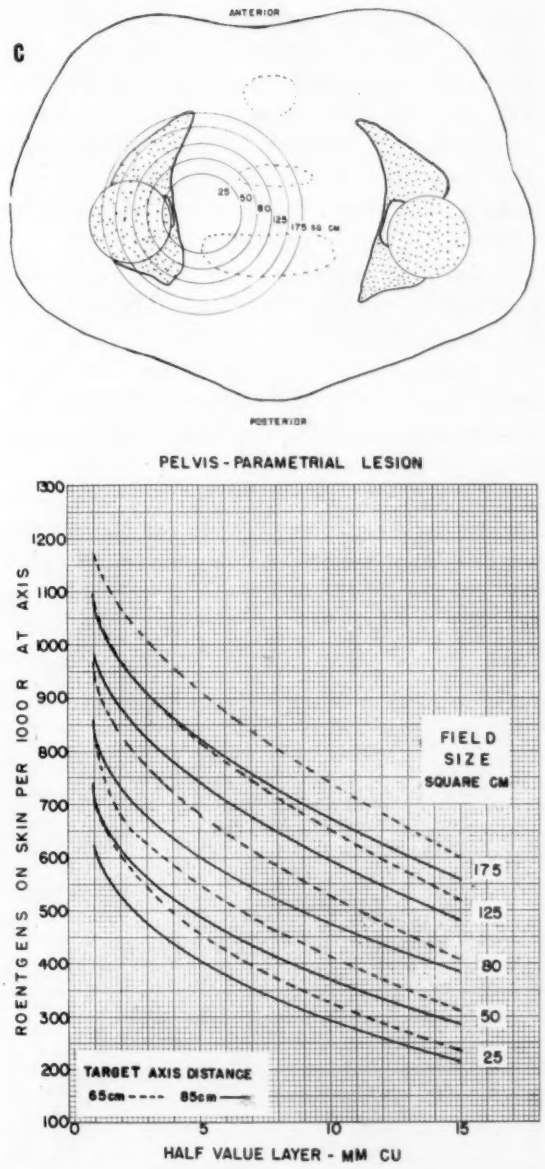

FIG. 5. Curves showing maximum skin dose per 1,000 r at axis, for lesions in average pelvis. (*A*) Cervix lesion. (*B*) Bladder lesion. (*C*) Parametrial lesion.

field larger than 50 sq. cm., part of the skin receives as much as the axis, or more, which is not tolerable. Increasing the distance to 85 cm. and the quality to half value layer 2.0 mm. of copper improves the situation considerably, but even in this case, with fields as large as 125 sq. cm., the maximum skin dose is about 90 per cent of the axis dose. Of course, the rest of the skin receives less radiation, but such therapy is drastic, and great care must be exercised to avoid complications due to irradiation of such a large part of the body to such a high level. At 4.0 mm. of copper half value layer ratios become more practicable, but it is obvious that for these large body sections supervoltage is a great advantage. At half value layer 15 mm. of copper (cobalt 60 radiation), even with the largest field and the shorter distance, the skin receives only 60–70 per cent of the axis dose, and with the longer distance somewhat less.

Increasing target-axis distance is often considered a good way to increase percentage depth dose, although it is appreciated that such increase is at the expense of increasing irradiation time. The curves of Figure 5 show that for all fields there is an appreciable improvement in increasing distance from 65 to 85 cm. It should be noted, however, that this improvement is somewhat greater for radiation of lower half value layers. From the data of Figure 7

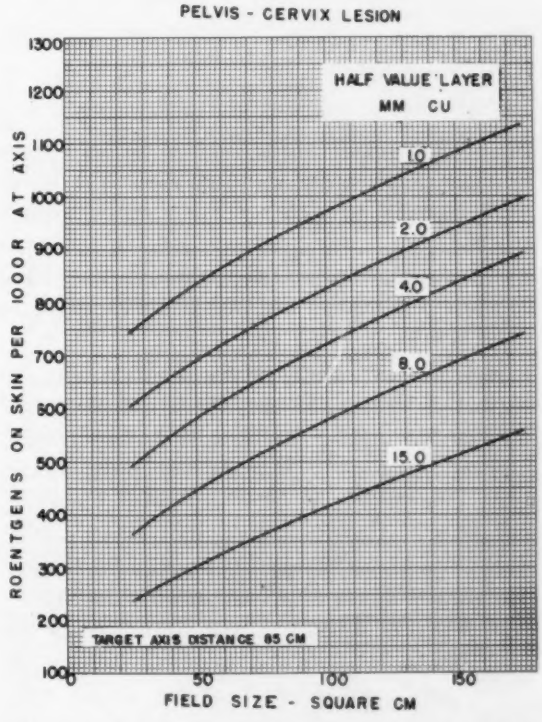

FIG. 6. Curves showing change in skin dose with field size for central pelvic lesion, for 1,000 r at axis in all cases.

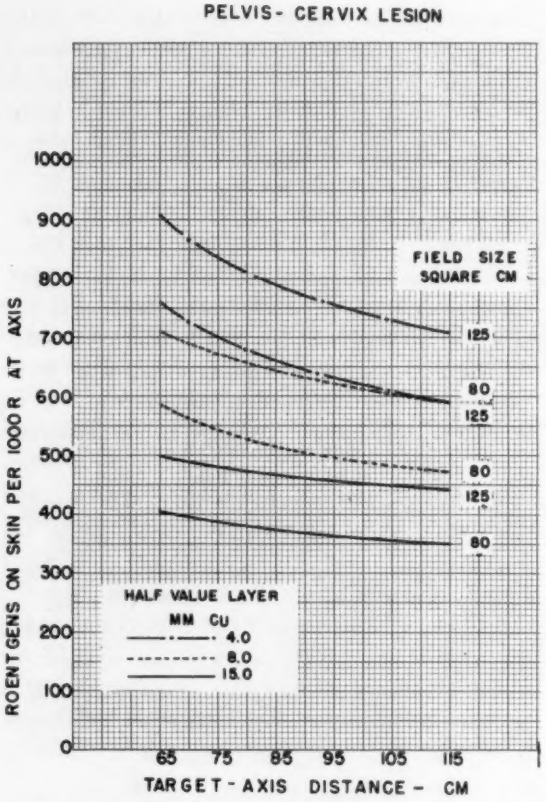

FIG. 7. Curves showing change in skin dose with target-axis distance, for central lesion in average pelvis.

it is apparent that improvement with further increase in distance is slow, whereas the time to deliver the required dose continues to increase rapidly. Unless very high radiation outputs are available, there is little advantage in increasing target-axis distance beyond 85 cm.

For smaller body sections it might be expected that skin-axis dose ratios would be more favorable because of the increased percentage depth dose at the axis. However, this proves to be not always the case, because of the increased exit dose. Similarly, for larger body sections, ratios may not be less favorable, because of decreased exit dose. In Figure 8 are shown data for two fields irradiating central lesions in three pelvic sections. For the larger field there is little difference in the ratios for the three sections when the lower half value layer radiation is used, but, as quality improves, the differential between skin and axis doses is greater the larger the section. For the smaller field, at low half value layers the advantage is with the smaller section but this is lost as the radiation becomes more penetrating. This should not be interpreted as a statement that for any cross-section whatever, a more favorable relation is obtained with radiation of low half value layer. The maximum skin dose per 1,000 r at the axis always decreases with increase in half value layer, but the decrease is faster for the large cross-section than for the small one.

For all sections and all distances there are no great differences in ratios for the various near-central locations. In all cases the effect of field size is very marked; the smaller the field the better the ratio. However, it is always a mistake to make the

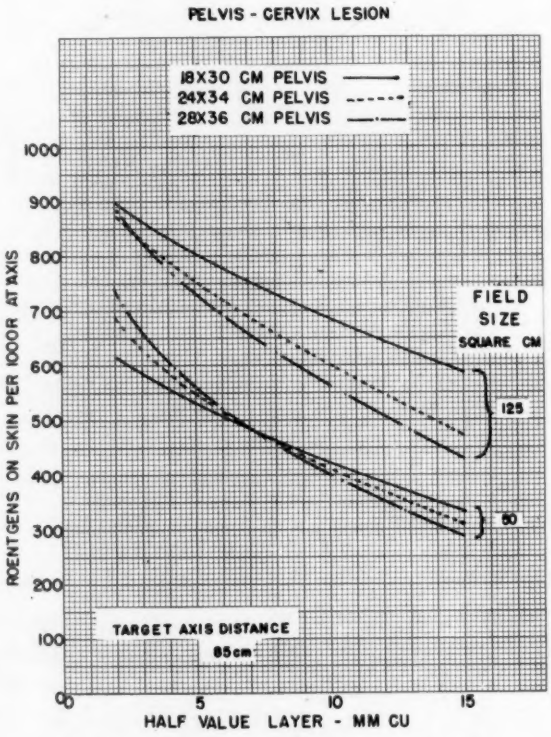

FIG. 8. Curves showing effect of area of pelvic section on relation between skin and axis doses for selected fields and various qualities of radiation. The axis of rotation passes through the cervix.

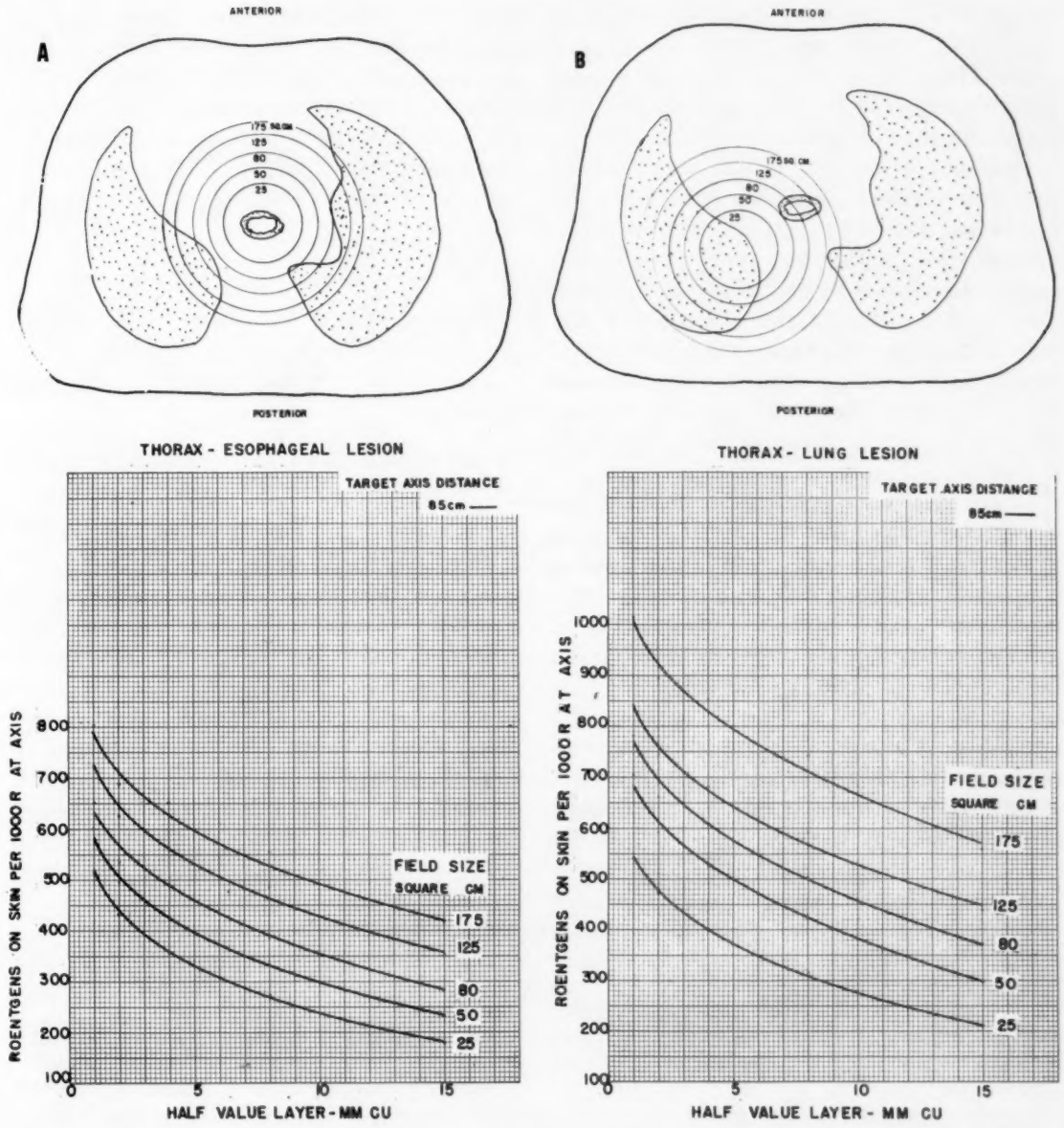

FIG. 9. Curves showing maximum skin dose per 1,000 r at axis for lesions in the average chest. Axis doses corrected for diminished absorption of radiation by lung tissue. (*A*) Esophagus lesion. (*B*) Lung lesion.

field smaller than the lesion, for then its periphery will be missed and the treatment will be unsuccessful.

LESIONS IN THORAX

Data for esophagus and lung are shown in Figure 9, for the 85 cm. target-axis distance only. These values were calculated in the same manner as the others and then axis doses were corrected by factors obtained from the special phantom as described above. If this correction were not applied, doses in the chest would be about the same as in the pelvis, for similar cross-section areas and the same physical factors. However, the actual difference is considerable. Also it is quite likely that fields used in the treatment of esophagus or lung

lesions will be narrower than those used in the pelvis, which results in a lower skin dose. Thus, in practice, ratios in thorax lesions are likely to be considerably more favorable than those in the pelvis.

Only the 85 cm. target-axis was used for the thorax study, since the results for the pelvis had shown the shorter distance to be undesirable except for very penetrating radiation. However, the effect of distance would be essentially the same as in the pelvis, and approximate ratios for a particular field and quality can be obtained from Figure 5. Similarly, an idea of the effect of size of the cross-section can be obtained from Figure 8.

It appears that most lesions in the chest should be amenable to rotation therapy with radiation of half value layer 2.0 mm. of copper and target-axis distance of 85 cm. Ratios for lesions in the lung are always somewhat worse than for the central position of the esophagus, but even for the lung lesion and a field of 125 sq. cm., the maximum skin dose is 750 r for 1,000 r at the axis, which is a satisfactory situation.

In all thorax calculations the arms were assumed to be up over the head, in order to make the transverse diameter as small as possible. If a patient cannot tolerate this position, and must have the arms at the sides, the diameter is increased by 10 to 20 cm., and the axis dose is much reduced. In this case it is probable that some other procedure than complete rotation is advisable.

OTHER ANATOMIC REGIONS

Data presented here for specific regions should furnish information regarding practicability of rotation therapy in other regions.

COMPARISON OF CALCULATED DATA WITH THOSE FROM THE LITERATURE

As stated above, much of the data in the literature is based on cylindrical phantoms. However, six papers were found with either complete rotation charts or skin-axis dose ratios for one or two anatomically correct body regions, each for a single quality of radiation.[1,2,3,5,6,7] Altogether these cover a range of qualities from half value layer 1.5 to 15.0 mm. of copper, and several sites in different parts of the body. Some of the doses were measured in unit

TABLE II

COMPARISON OF DATA ON RATIOS BETWEEN MAXIMUM SKIN AND AXIS DOSES

Author	Anat. Region and Cross-section Dimensions	Half Value Layer	Target-Axis Distance	Field Size	Skin Dose / Axis Dose	Compare with Our Text Figure	Our Ratio for Approx. Same Conditions
	cm.	mm. Cu	cm.	cm.	per cent		
Hawley[3] (Meas. Ion. Ch.)	Ellipse 30×40	1.8	65	7×20	70	7	68
Trump *et al.*[7] (Meas. Films)	Pelvis 23×36	2 mev.	108	15×15	50	6	53
Thomas *et al.*[6] (Meas. Ion. Ch.)	Phantom with bones 19×36 (very flat)	3.5	85	5×15	35	4	50
				10×15	55	4	73
Johns *et al.*[5] (Calc.)	Chest unit density size not given	2.0	60	8× 8	80	8	84 (no lung correction)
Braestrup and Mooney[1] (Calc.)	Pelvis 20×30	15.0 (Co^{60})	75	6× 6	28	7	25
Castro *et al.*[2] (Calc.)	Chest unit density 24×32	1.5	85	10×10	68	8	78 (no lung correction)

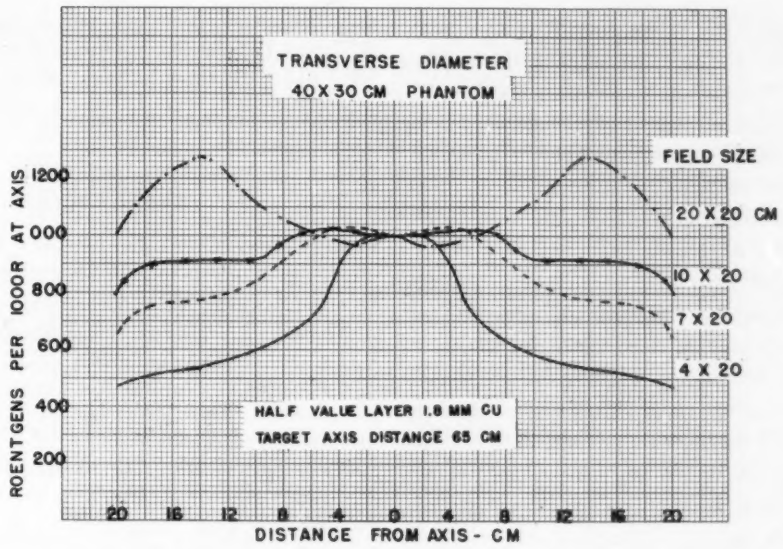

FIG. 10. Curves showing distribution of dose from axis to skin for various field sizes. Half value layer 1.8 mm. Cu. Target-axis distance 65 cm. (Data courtesy of Dr. Sydney Hawley.)

density phantoms, others were calculated by various methods. Few of the cross-sections or fields were exactly the same as ours, but it is interesting to compare the data as nearly as possible. This is done in Table II. Considering the variations in shapes of phantoms and fields, agreement is good. This lends support to the conclusions presented in this paper.

It must be understood that skin-axis dose ratio is not the only factor to be considered in deciding about the use of rotation therapy. The entire dose distribution pattern is important.

Complete dosage patterns are outside the scope of the present paper, but some general statements may be made. When the tumor-bearing region situated near the center of the body can be covered by a relatively small field, the dose within this volume is always greater than anywhere outside it. The dose gradient between this region and the body surface is quite rapid, especially for relatively hard radiation. As the irradiated volume is increased, the decrease in dose outside it is slower. For supervoltage radiation there is almost always a good demarcation, but as the radiation becomes softer the differential becomes less and may vanish completely. For large fields and soft radiation it has been shown earlier that the skin dose may exceed the axis dose; in this case the dose gradient from tumor outward is an increase rather than a decrease. In Figure 10 are shown curves from measured data for radiation of half value layers 1.8 mm. of copper published by Hawley[3] illustrating these considerations. By comparing these curves with data from our Figures 3–9, it can be seen that where the skin-axis dose ratio is low, the entire curve should be quite satisfactory; when it is high, the entire distribution is undesirable.

SUMMARY

Calculated values of the ratio of maximum skin dose to axis dose in rotation therapy are presented for lesions in various positions in head, pelvis, and chest. Radiation qualities cover a range of copper half value layers from 1.0 to 15.0 mm., the last corresponding to the radiations from radioactive cobalt 60. Target-axis distances of 65 and 85 cm. are used for most problems, and 115 cm. for a few. A suitable range of field sizes is studied for each anatomic location.

Lesions in the interior of the head can be adequately treated with roentgen rays of

relatively low half value layer and short target-axis distance. Improvement in the ratio of skin to axis dose with increase in either half value layer or distance is slow but definite. It is seldom necessary to take advantage of this improvement.

For lesions in the average pelvis, it is essential to use at least 2.0 mm. of copper half value layer and a target-axis distance of 85 cm. Increasing the half value layer to 4.0 mm. of copper or the distance to 115 cm. gives better ratios. However, in these cases, supervoltage radiation is of great advantage. For patients with smaller cross-sections, benefit with improved physical factors is less marked than for those of larger dimensions.

In the chest, diminished absorption of radiation by lung tissue leads to higher depth doses. Because of this, adequate treatment of many lung and esophagus lesions can be carried out with half value layer 2.0 mm. of copper and 85 cm. target-axis distance. However, here also the advantage of supervoltage is marked.

Edith H. Quimby, Sc.D.
630 W. 168th Street
New York 32, New York

We wish to express our thanks to Miss Ginette Jacob for assistance in the dosage measurements with the phantom, and to Dr. Sydney Hawley for permission to use his data for Figure 10. We are grateful to the American Cancer Society for the grant which made this study possible.

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DEVELOPMENT AND TRANSPLANTATION OF LOCALLY RADIORESISTANT MOUSE LYMPHOMA*

By CHARLES M. NICE, JR., M.D., M.S., PH.D.
MINNEAPOLIS, MINNESOTA

THE development of spontaneously induced or acquired resistance is a commonly observed phenomenon in nature. Bacteria, protozoa and tumor cells have been noted to develop a state of refractoriness or resistance to the action of various agents to which they had previously responded. Much speculation has arisen concerning the mechanism by which the state of resistance occurs, and both clinical and experimental observations have been cited in favor of various theories.

In the presence of antibiotics, bacteria are said to develop a gradual, step-wise, "penicillin pattern" or a "streptomycin pattern" of resistance in which the degree of resistance varies greatly in the first-step mutants.[1] Leukemic cells in mice are said to develop a gradual, step-wise or "penicillin pattern" of resistance against chemical antagonists. In most instances, the acquired state of resistance is said to be relatively specific, stable, heritable and irreversible.[3] It has also been suggested that the change to the state of resistance occurs independently of the action of the antagonist.[1,3]

Most observers have stated that the state of acquired resistance is due to selection, spontaneous or induced mutations, or in the case of acquired resistance to irradiation by tumors, to tumor bed injury. Windholz[7] observed cytologic metaplasia in irradiated laryngeal carcinoma in human subjects and considered this the basis for acquired radioresistance. Schubert[5] cited experimental evidence that led him to believe that acquired radioresistance in transplantable Ehrlich carcinoma in mice is due to induced tumor cellular mutations.

Kirschbaum[2] induced refractoriness to potassium arsenite therapy in a transplanted mouse leukemia by treatment of the host with the drug prior to transplantation of the tumor cells. Montgomery and Warren[4] failed to induce resistance by irradiating lymphosarcoma cells *in vitro* between successive transplantations in mice and concluded that acquired radioresistance is not a function of the tumor cells. Based on clinical observations, Sturgis[6] gave the opinion that acquired resistance to irradiation in human leukemia is due to increase in extent of the disease.

Because of the conflicting opinions cited above, it seemed pertinent to attempt to determine whether the acquired resistance to irradiation as exhibited by tumors is due to a change in the tumor cell population or to a change in the tumor-host relationship.

DEVELOPMENT AND TRANSPLANTATION OF MOUSE LYMPHOMA EXHIBITING ACQUIRED RESISTANCE TO IRRADIATION

It was decided to study acquired resistance to irradiation in mouse lymphoma by attempting to duplicate acquired resistance as it is seen clinically. It is common knowledge that leukemic and other lymphomatous masses may respond to irradiation, only to recur and resist further irradiation. For these experiments line 1016 leukemic cells in strain F mice were utilized.

A. *Line 1016 Lymphatic Leukemia.* Line

* From the Department of Radiology, University of Minnesota Medical School, Minneapolis, Minnesota. Presented at the Fifty-seventh Annual Meeting of the American Roentgen Ray Society, Los Angeles, California, September 25–28, 1956. This material is an abridgement of part of a thesis submitted to the University of Minnesota Graduate School in partial fulfillment of the requirements for the Doctor of Philosophy degree in Radiology. This research was supported by the institutional grant from the American Cancer Society.

1016 leukemia cells originated spontaneously in a mouse so-numbered in Kirschbaum's strain F colony. In the early transfers, subcutaneous inoculation resulted in the formation of a tumor which remained localized for a few days after it became grossly palpable and visible. Untreated animals died of disseminated disease between eleven and thirty days after inoculation. In later transfers the tumor became more virulent and had become disseminated by the time the local tumor was macroscopically evident.

For transplanting, the tumor tissue was dissected out immediately after the animal had been sacrified by fracturing the cervical spine or by the use of ether anesthesia. The tumor tissue was then minced with sharp scissors in sterile 0.85 per cent sodium chloride solution until a uniform cell suspension was obtained. A random cell count on such a suspension gave 32,000 cells per cubic millimeter. The cell suspension was aspirated into a tuberculin syringe and injected into the subcutaneous tissue of the right flank. Usually 0.02–0.04 milliliter produced a visible wheal and this was considered a satisfactory transplant.

When the experiment was started, the relative sensitivity of the tumor to irradiation was not known. It was found that a dose of 500 r in air of local irradiation or a dose of 300 r in air of total body irradiation caused such a response that a tumor 1 cm. in diameter was not palpable or visible twenty-four to forty-eight hours later. That this dose was not lethal for the tumor was evident since the tumor recurred and had again attained a diameter of 1 cm. in three to four days. For local irradiation the mice were anesthetized by intraperitoneal injection of 1 per cent sodium amytal and the untreated portion of the animal's body was protected by a shield of lead 2 mm. thick which absorbed over 98 per cent of the radiation employed. For total body irradiation the mice were simply confined in cardboard boxes of 2 mm. thickness; this thickness of cardboard absorbed only a negligible amount of the radiation employed.

Irradiation factors were: 140 kv. peak, 30 cm. target-skin distance, 4 ma., and 2.0 mm. Al filter (half-value layer 4.2 mm. Al).

Results. Two mice constituting the first generation of this experiment were treated with 500 r in air locally when the tumor was approximately 1 cm. in diameter. After twenty-four hours there was no macroscopic evidence of local tumor. Within four days the tumor had recurred to attain a diameter of 1 cm., when the same dose of local irradiation produced a similar response. Five days later the tumor had again recurred in 1 mouse and failed to respond to 500 r in air locally. This tumor was then transplanted to 3 previously untreated animals. The other animal had a recurrent tumor of 1 cm. in diameter eleven days after the second roentgen exposure and also exhibited local resistance to irradiation. Five days later the animal died of disseminated disease.

Two of the mice in the second generation of this experiment were treated with successive doses of 500 r locally in the same manner as those described in the first generation. Three times each tumor attained a diameter of 1 cm., and each time there was no macroscopic evidence of local tumor twenty-four hours after the administration of 500 r locally. Both animals died of disseminated disease. Thus, although the tumors failed to attain a state of local resistance to irradiation, the repeated sequences of local tumor growth and regresssion allowed the disease to become generalized.

The third mouse of this group was not treated and the tumor was transplanted into 5 fresh mice in order to preserve the line of cells from the tumor which had attained resistance to local irradiation in the first generation.

The mice in the ensuing third to seventh generation of this experiment were all treated with 300 r total body irradiation. When the transplanted tumor attained

a diameter of 1 cm., the 5 mice were treated with this dose and twenty-four hours later there was no macroscopic evidence of tumor. After the third treatment there was no local response to irradiation and the tumor was transplanted into 5 mice of the fourth generation.

In the 5 mice of the fourth generation the response was identical to that seen previously. After the third treatment the locally resistant tumor was transplanted into 5 mice of the fifth generation.

In the fifth generation of mice the tumor was definitely over 1 cm. in diameter when the first dose of 300 r total body irradiation was given. All of the tumors decreased in size, but there was still macroscopic evidence of local tumors at twenty-four and forty-eight hours after treatment. It was reasoned that the cells had become relatively more resistant due to selection or mutation or that the larger tumors were more resistant than the tumors of 1 cm. in diameter. To pursue this question, one of the tumors was transplanted into 5 mice of the sixth generation.

When the tumors of these 5 mice attained a diameter of 1 cm., a dose of 300 r total body irradiation was given. In each mouse there was no macroscopic evidence of local tumor twenty-four hours after irradiation. Again local resistance was exhibited after the third treatment and one tumor was transplanted into 5 mice of the seventh generation.

The same pattern of response was noted in each of the 5 mice of the seventh generation. After three treatments there was still partial response as denoted by a slight decrease in the size of one tumor. This tumor was transplanted into 5 more mice, which would have constituted the eighth generation, but the tumor failed to grow in any of these mice. On no other occasion did this line of tumor cells, treated or untreated, fail to grow when transplanted into as many as 5 animals.

The results of this experiment are illustrated graphically in Figure 1.

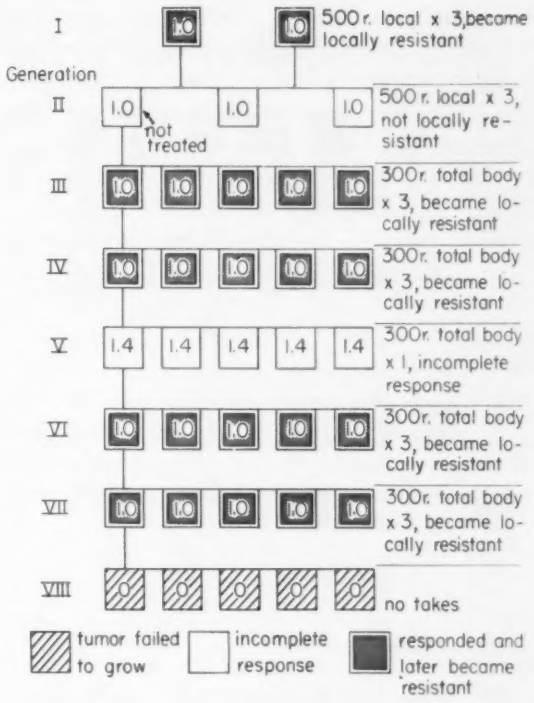

Fig. 1. Line 1016 leukemia acquiring local resistance after repeated irradiation, sensitive after transplantation.

B. *Gardner Lymphosarcoma.* When strain F mice were no longer available to the author, it was decided to try a similar experiment with another tumor. The Gardner line of lymphosarcoma was available, but the mouse strain in which it arose was not available at the time. However, it was found that the tumor would grow locally for three weeks or longer before metastasizing when transplanted in the flank of CBA mice. Therefore, the response to irradiation was tested.

It was found that when a local tumor of 1 cm. in diameter was treated locally with doses ranging from 200 r to 1,000 r the tumor exhibited no response in some mice, decreased from 1 to 9 mm. in diameter in a second group and was eradicated completely in still a third group.

Two experiments were performed utilizing the Gardner lymphosarcoma in CBA mice. In the first experiment, a tumor was transplanted which at first responded to 200 r of local irradiation. Subsequently, the tumor was refractory to the same dose.

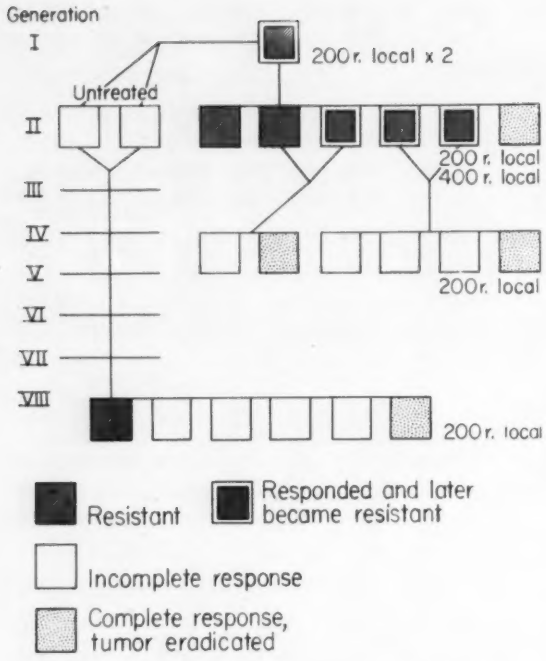

Fig. 2. Gardner lymphosarcoma. First experiment on radioresistance.

Upon transplanting this locally resistant tumor through two treated generations of mice, the tumor was found to be sensitive to a dose of 200 r locally. After transplanting the original tumor with acquired resistance through six generations of untreated mice, the tumor was again shown to be sensitive to 200 r locally (Fig. 2).

In the second experiment with Gardner lymphosarcoma, 17 mice with tumors approximately 1 cm. in diameter were treated with 400 r locally. Of these, the tumor was eradicated in 2 mice, partially responded in 11 mice, and showed no measurable response in 4 mice. Two tumors originally showing a partial response subsequently became refractory to treatment and were transplanted into 18 mice. Of these, the tumor was eradicated in 3 mice and partially responded in 15 mice. One of the tumors partially responding later became resistant to 400 r locally and was transplanted into 8 previously untreated mice. Three of these tumors were eradicated by 400 r, three responded partially and two exhibited no response.

After being treated in three successive generations with a total dose of 2,800 r, one tumor was transplanted into 10 previously untreated mice. In 4 of these mice the tumor was eradicated by 400 r locally, and in 6 mice there was partial response. After allowing the tumors to enlarge again to a diameter of 1 cm., the second dose of 400 r eradicated five of the six remaining tumors.

The single remaining tumor of the fourth generation of mice was transplanted to 6 mice of the fifth generation. The first dose of 400 r eradicated one tumor and caused a partial response in the others. When these five again grew to a diameter of 1 cm., they exhibited resistance to the second dose of 400 r.

One of these tumors was then transplanted to 8 mice of the sixth generation of this experiment. The first dose of 400 r eradicated five tumors, and the second dose of 400 r eradicated two more tumors. The eighth tumor did not respond to the second dose.

This remaining tumor, which had been exposed to a total of 4,400 r in six consecutive transplant generations, was then transplanted to 12 mice of the seventh generation. The first dose of 400 r eradicated six tumors and caused a decrease in

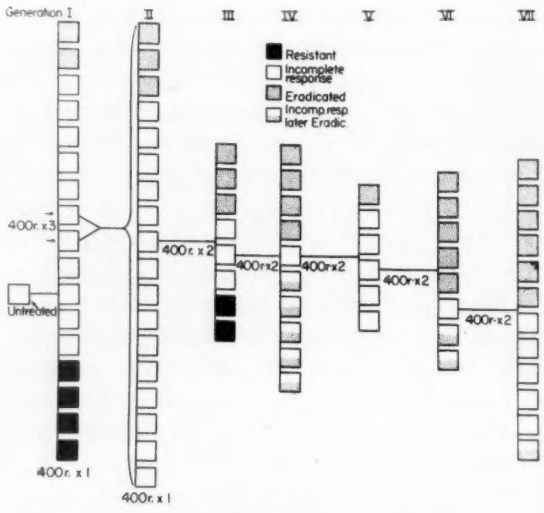

Fig. 3. Gardner lymphosarcoma. Second experiment on radioresistance.

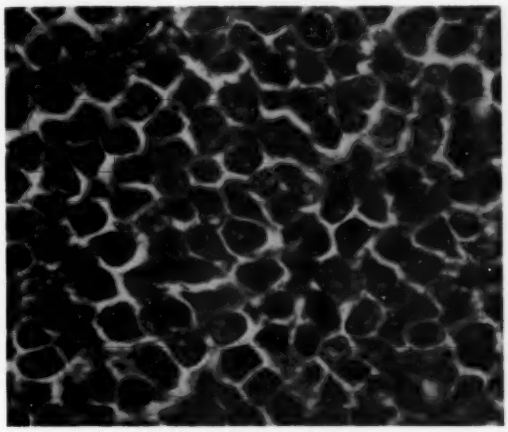

Fig. 4. Untreated Gardner lymphosarcoma (×600).

size in the other six tumors. When these tumors again reached 1 cm. in diameter, the second dose of 400 r eradicated one more tumor. The results of this experiment are tabulated in Figure 3. The resistant tumors are being transplanted to continue the sequence in order to ascertain whether the tumor cells will eventually become resistant when transplanted into previously untreated mice.

As an additional note of interest, Dr. Robert Hebbel, Associate Professor of Pathology at the University of Minnesota, examined several histologic sections of a previously untreated Gardner lymphosarcoma and compared these with sections of a tumor exhibiting acquired local resistance to irradiation. No histologic difference was found (Fig. 4 and 5).

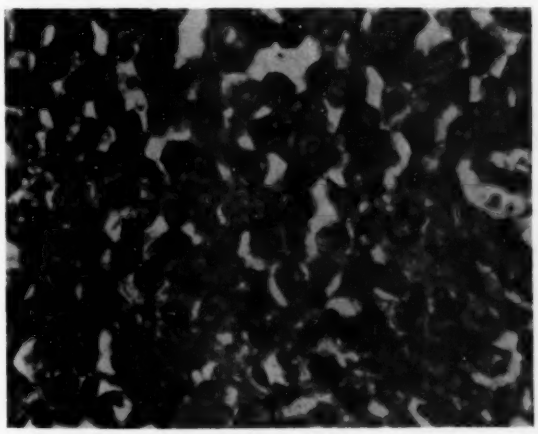

Fig. 5. Resistant Gardner lymphosarcoma (×600), from second experiment. This tumor had responded partially to 400 r in the first generation of mice, becoming resistant after the third treatment. The tumor was then transplanted into previously untreated mice, and again showed a partial response to 400 r. After the second treatment the tumor shown above again proved refractory to 400 r locally.

DISCUSSION

These experiments appear to indicate that acquired local resistance to irradiation in lymphoid tumors in mice is not a function of the tumor cell population. In other words, acquired local resistance to irradiation is not due to a process of selection nor to induced tumor cellular mutations.

These observations may be of value in clinical roentgen therapy. If nothing more, they would seem to lend support to the idea of using intensive roentgen therapy in apparently localized lymphomatous masses. Many times these two tumors in these two strains of mice appeared to disappear macroscopically, only to recur shortly thereafter and then exhibit acquired local resistance to irradiation.

If it can be accepted that acquired local resistance to irradiation is not a function of the tumor cells *per se* the question arises as to what other mechanisms might be involved. In this laboratory it has been demonstrated that the response of previously untreated mouse lymphosarcomas to irradiation varies with the size. It could well be that increased size of tumor or progression of the disease may be one of the factors operating in acquired local resistance to irradiation. Other factors to be considered are the effects of irradiation on the tumor bed and humoral factors. Experiments are being designed in an attempt to assess these latter possibilities.

SUMMARY

Acquired local resistance to irradiation occurs when a tumor which previously responded to a given dose of irradiation no longer responds to subsequent administration of the same dose of the same agent.

Experiments have been described herein in which line 1016 lymphatic leukemia in strain F mice and Gardner lymphosarcoma in CBA mice were exposed to responsive doses of irradiation, after which the tumors recurred and exhibited acquired local resistance to similar doses of irradiation. When these tumors were transplanted to previously untreated mice, the response to irradiation was similar to that observed in previously untreated tumors. This finding was constant in seven transplant generations of mice with both tumor lines.

In both the previously treated and previously untreated tumors the response to irradiation decreased with increasing tumor size.

CONCLUSIONS

Acquired local resistance to irradiation in line 1016 lymphatic leukemia transplanted in strain F mice and in Gardner lymphosarcoma transplanted in CBA mice is not a function of the tumor cells, that is, it does not arise as a result of selection or induced mutations in the tumor cells.

The response of these mouse lymphomas to irradiation varies with the size of the tumor, indicating that increased tumor size or progression of disease could be one of the factors operating in acquired local resistance to irradiation.

The importance of radiation injury to the tumor bed and humoral mechanisms remains to be evaluated.

University Hospitals
Minneapolis, Minnesota

ADDENDUM

Before this paper went to press the second experiment utilizing Gardner lymphosarcoma cells in CBA mice was continued through ten generations. The response in the tenth generation was essentially the same as in the first generation.

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THE EFFECT OF IONIZING RADIATIONS ON THE REGENERATION AND BEHAVIOR OF MAMMALIAN LYMPHATICS*

IN VIVO STUDIES IN SANDISON CLARK CHAMBERS

By H. A. S. VAN DEN BRENK, M.S., F.R.C.S., D.T.R.†
MELBOURNE, AUSTRALIA

THIS paper deals with observations *in vivo* on the regeneration and behavior of lymphatics in repair tissue in the rabbit following the administration of ionizing radiations.

LYMPHATIC REGENERATION IN REPAIR TISSUES

Unequivocal evidence that lymphatics regenerate in mammalian repair tissues was provided by Clark and Clark[9] using the "round table" type of Sandison Clark ear chamber in the rabbit. The growth and behavior of lymphatics was observed *in vivo* and supplementary studies were made later (Clark and Clark,[10–12] Henry[16]). Prior to this account of lymphatic regeneration in mammals, a systematic study *in vivo* of lymphatic regeneration in amphibian larvae had been made by Clark.[5–7]

Before the studies of the Clarks, less conclusive evidence provided by histologic and injection studies suggested that the regeneration of lymphatics in repair processes did occur. Billroth[3] demonstrated lymphatic regeneration by injection in a wound in the dog's lip. Other authors using injection techniques demonstrated lymphatics in or near granulation tissue (Poirier,[22] Guyot,[15] Vecchi,[31] and others). A micro injection technique in the living animal devised by Smith and Rous[26] has been used successfully in the mouse's ear by McMaster and Hudack,[19] and Pullinger and Florey[23,24] to demonstrate lymphatic reactions to injury and certain stimuli and has provided further positive evidence for the regeneration of lymphatics in mammals.

BEHAVIOR OF REGENERATING AND FORMED LYMPHATICS IN REPAIR TISSUE

Detailed descriptions of the behavior of individual lymphatics followed *in vivo* over long periods during regeneration and after certain types of injury have been given by the Clarks. These studies afford most of the reliable information concerning lymphatic regeneration and behavior in response to injury. Certain aspects of this work will be described briefly insofar as studies to be reported are concerned.

1., Lymphatics regenerate as solid endothelial protrusions which grow out in continuity from pre-existing lymphatics, and subsequently become cannulated. In tissues which are undamaged, the lymphatic system is a closed system lined by a single layer of endothelium. This endothelium is derived in regeneration from pre-existing lymphatic endothelium and has not been observed to arise by metaplasia from either vascular endothelium or the mechanocyte tissues comprising the rest of the blastema. This finding, which supports Flexner's law for tissue specificity in regeneration, was inferred by Ranvier.[25] There is no evidence that lymphatics arise in regenerates by the transformation of perivascular spaces, the "extraintimal theory of origin" of Huntington and McClure,[17] nor that they arise by coalescence of spaces in the mesenchyme—a view subsequently held by Huntington and McClure.

2. The actual tactics of growth underlying lymphatic regeneration at a cellular level have not been completely elucidated. The

* From the H. N. Smith Research Unit, Department of Applied Physiology, Royal College of Surgeons of England.
† Late Senior H. N. Smith Research Fellow, Department of Applied Physiology, Royal College of Surgeons of England.

Clarks describe the importance of endothelial migration and the lability of nuclei in the formation and extension of lymphatic buds or protrusions. They also describe mitosis in lymphatic endothelium. Studies of lymphatic growth in Sandison Clark chambers by the writer confirm the importance of endothelial migration and nuclear lability in the growth of endothelial buds, but the unequivocal observation of mitosis occurring in lymphatic (or vascular) endothelium has not been made. The close apposition of endothelial nuclei and their subsequent migration, "overtaking," or attenuation is readily observed, but clear division of a parent nucleus with separation of daughter nuclei has not been seen. The extremity of the elongated growing lymphatic bud may contain one or two nuclei, but usually consists entirely of cytoplasm, with subsequent migration of nuclei into the tip, to be followed by further cytoplasmic extension. While endothelial mitosis must indubitably occur in regeneration of lymphatics, it is clear that as for vascular regeneration (van den Brenk[29]), the "*tactics* of regeneration, as of embryonic development, is primarily and fundamentally a matter of movement of cell substance, cells and cell groups. It is not primarily a matter of cell division, nor of synthesis in general, though in due course these are called upon to play their part" (Medawar[20]).

3. Lymphatics tend to assume a perivascular position, owing to the relative absence of connective tissue adjacent to vessels and the presence of a perivascular space. If for any reason, trauma, inflammation, or abnormal stresses due to warping of the chamber take place, increased fibrous tissue forms and maturates in a regenerate, and the latter acts as a serious impediment to the growth of lymphatics (Clark and Clark[11,12]). It has been shown that this also applies to vascular regeneration in irradiated regenerates (van den Brenk[30]). Fibrous tissue can in this way lead to constriction of a lymphatic with isolation of a lymphatic segment; such a segment may remain for many months as a closed fragment or subsequently grow and unite with another portion of the system (Clark and Clark[12]).

When a growing lymphatic tip meets an obstruction to growth caused by either dense fibrous tissue or the tissue barrier formed by larger branching blood vessels, further migration ceases and the lymphatic sprout becomes rounded in shape.

4. A regenerate can successfully survive with no abnormal morphologic changes taking place in the absence of lymphatic regeneration. This state of affairs is particularly seen in the tantalum type ear chamber (Williams[32]) in which lymphatics fail to regenerate. The reason for the latter observation is not clear but apparently lymphatics do not possess the same lability as blood vessels in penetrating the tantalum gauze former, with changes in direction of the axis of growth. Also it must be stressed that lymphatics fail to regenerate in ear chambers in which (a) the tissue space is too thin—less than 70 μ and (b) warping occurs and results in abnormal chronic tissue tensions giving rise to the excess development and maturation of fibrous tissue in the regenerate (Clark and Clark[11]).

5. If a tissue becomes "inflamed" due to bacterial infection, the preformed lymphatic system present not only dilates but responds by intensive proliferation, with the formation of a rich lymphatic plexus. It is emphasized that this parallels changes in the vascular bed. The latter not only dilates with opening up of capillaries previously closed, but marked proliferation of capillaries takes place—a feature of inflammation which has not been given sufficient emphasis. The proliferation of lymphatics in inflammation caused by turpentine, pyogenic cocci, barium sulphide, amorphous silica and carcinogenic tar has been elegantly demonstrated by Pullinger and Florey[24] in the living mouse's ear using injection techniques. When the inflammation subsides, regression of lymphatics takes place with a reduction in

density of the lymphatic plexus which approaches the stable state.

6. While edema of tissues is accompanied by a local dilatation of the lymphatic plexus, it has been demonstrated that lymphatics fail to react to adrenalin, pitressin or direct mechanical stimulation (Pullinger and Florey[23]).

7. If a lymphatic is locally obstructed and becomes isolated, it may persist in this condition for long periods or link up with the patent system elsewhere. In the former event, the isolated segment fails to dilate, but may remain unchanged for months or undergo slow regression. Any cells or debris contained in such an isolated segment neither "stick to the walls" nor are phagocytosed by the endothelium, but appear to gain considerable protection (Clark and Clark[11]). Also, in inflamed blood vessels in an ear chamber, gross leukocyte "sticking" to the vascular endothelium takes place, but this does not take place in the lymphatics, suggesting an essential difference in the nature of the two types of endothelium (Clark and Clark[11]). Lymphatic endothelium in mammals does not possess the ability, exhibited by lymphatics in amphibians, to engulf and remove foci of hemorrhage and tissue debris following injury (Clark and Clark[11]). In mammals this function is essentially performed by the systemic recruitment of macrophages from monocytes and by the more limited but similar functions of histiocytes (Ebert and Florey[13]).

8. If a lymphatic capillary suffers local injury with a rupture of its endothelial wall, the hole may persist for several days with free interchange of fluid and cells between the outside tissue and the capillary lumen (Clark and Clark,[10] Henry[16]). This is not observed in the blood vessel endothelium, rupture being accompanied by endothelial retraction and thrombosis. The histologic demonstration that reticulum and collagen fibers from surrounding tissues adhere to the lymphatic endothelium (Pullinger and Florey[23]) is significant in this regard.

EFFECTS OF IONIZING RADIATIONS ON THE REGENERATION AND BEHAVIOR OF LYMPHATICS

As far as has been ascertained, no systematic observations on the effects of ionizing radiations on the growth and behavior of lymphatic vessels has been made. The descriptions by Borak[4] of changes in lymphatics following irradiation is almost entirely based on analogy and inference. Borak gives detailed cellular descriptions of changes in lymphatics without direct experimental facts to justify his conclusions. As a typical example, he refers to three phases of "lymphatic dilatation" corresponding to erythema waves, based on observations of clinical edema following irradiation.

Experimental studies conducted to determine the effect of ionizing radiations on the flow of lymph give conflicting results. Sugarbaker and Sugiura[27] showed that the transport of injected India ink to lymph nodes in rats after local irradiation is reduced. They suggest that lymphatics are neither damaged by irradiation, nor is the flow increased. In rabbits Painter[21] *et al.* demonstrated an increased spread of Evans blue, injected intradermally into irradiated skin, during the first few hours, which they consider presumptive of an accelerated lymph flow. In human skin Ané and Burch[1] reported no change or a decrease in the cutaneous lymph flow with moderate to large doses. Certain experimental results pertain to the effects of total body irradiation on thoracic duct outflow. In the cat, Valentine *et al.*[28] reported little change during the first few hours after irradiation, and Bigelow *et al.*[2] recorded an increased lymph flow in the dog several days after total body irradiation.

The significance and interpretation of the presence of blood cells in the lymph following local and total body irradiation in rats and dogs (Furth *et al.*,[14] Bigelow *et al.*,[2] Wish *et al.*[33]) is open to speculation. The possibility that this finding may be due to causes other than direct damage of vascular and lymphatic endothelium must

be considered in view of the cytocidal effects of low dosage irradiation of lymph nodes and the extensive erythrophagocytosis and hemosiderosis found to take place in the lymph sinuses (Furth *et al.*[14]).

In the studies which are to be presented, a preliminary attempt has been made to elucidate certain fundamental problems:

1. The threshold dose of ionizing radiations which inhibits the regeneration of lymphatics in mammalian repair tissue.
2. Whether the "inflammatory changes" which accompany irradiation of tissues resemble inflammation due to certain other damaging agents (for example, bacterial infections, chemicals, carcinogens, etc.) in causing intensive lymphatic proliferation.
3. The effect of irradiation on a preformed or mature lymphatic plexus.
4. The response of irradiated lymphatics to certain vasotropic drugs.
5. Whether the cellular contents and flow in irradiated lymphatics present any abnormalities.
6. Whether irradiated lymphatics dilate if the parent tissue becomes edematous.

ALTERNATIVE METHODS OF STUDY

Clearly, an *in vivo* technique is essential which will enable the study of individual lymphatics at a cellular level over long periods of time. For this purpose, two ear chamber techniques have been adopted: (a) A modified all-perspex Sandison Clark ear chamber of the "round table" type with a 100 μ thick space, allowing for uniform irradiation of the regenerating tissues (van den Brenk[29,30]) and (b) a modified preformed ear chamber of similar construction utilizing the mature preformed tissues of the rabbit's ear. This method enables a clear demonstration of lymphatics and their reaction to systemic and locally applied stimuli.

These techniques are preferable to *in vivo* injection methods—continuous observation over long periods is allowed and without the error introduced by the forcible injection of colored solutions (hydrokollag, Evans blue, etc.) into a lymphatic plexus, which precipitates trauma and physical alterations on each occasion observation is necessary.

EXPERIMENTAL METHODS

1. A preliminary series of 30 ear chambers in rabbits which regenerated were observed, and the development of lymphatics followed. As in subsequent experiments the animals used were adult semi lop-eared rabbits, 2–4 kg. in weight, housed in separate cages in a constant temperature environment (70° F. $\pm$ 2° F.) and fed on a standard diet (Bruce and Parkes No. 2). Observations of the growth of the lymphatics confirmed the detailed studies of the Clarks, although attention has already been drawn to the emphasis on endothelial migration as the kinetic tactics of growth in both lymphatics and blood vessels (van den Brenk[29]).

2. In a further series of 80 ear chambers managed under identical conditions after growth of the repair blastema had commenced, a *single tissue dose* of irradiation was administered as gamma rays from a Co^{60} source, the dose employed ranging from 200 to 4,000 gamma roentgens. The subsequent cellular changes in the blastema were observed, recorded and photographed, *in vivo*, over periods up to 15 months after irradiation. In some of these chambers, irradiation was not given until varying periods after completion of growth. In others, if infection occurred, the tissue reactions were carefully noted. In a few nonirradiated but infected round table type chambers, the inflamed tissues were irradiated and the changes observed. In other irradiated chambers, edema was induced by intermittent mechanical pressure, and the tissue reactions observed. The study of these chambers has been carried out not only by prolonged direct microscopic observation *in vivo* in the intact unanesthetized animal, but also using additional techniques, namely, electronic flash photography to "freeze" movement of blood, photography by polarized light for

the demonstration of fibrous tissue, phase contrast photomicrography, and intravital techniques for the demonstration of nerve regeneration and macrophage-histiocyte systems.

3. A series of 19 preformed ear chambers were studied, particularly with reference to the effects of ionizing radiations on the vessels and lymphatics and the reaction of vessels and lymphatics to certain vasotropic drugs before and after irradiation. This type of chamber utilizes the preformed tissues of the rabbit's ear. In a one stage operation after reflection of the skin flaps using the ordinary aseptic technique for round table type ear chambers (van den Brenk[29]), a circle of cartilage is removed to fit the central table, but leaving behind the perichondrium and overlying vessels and lymphatics. The thick tissue space in these chambers (150–200 μ) does not allow for cellular detail but provides excellent means for the observation of blood vessels, lymphatics and nerves with transmitted filtered light. Drugs were administered intravenously in the opposite ear and the chamber area photographed at various times before and after injection. The doses of drugs used were adrenalin (1 to 100 γ), nor-adrenalin (10 to 100 γ), pitressin (5 to 10 pressor units), histamine phosphate (500 γ), acetyl choline (10 γ), phenyl-1-butyl nor-suprifen ("dilatal") (0.25 to 0.50 mg.), "priscol" (1 to 2 mg.), and amylnitrite (by inhalation).

Irradiation of Chambers—Physical Aspects. A Co^{60} foil source (75 mc, 3 cm. in diameter) fitted to a perspex applicator was used as a "sandwich" mold to irradiate the central table (6 mm. in diameter) and the surrounding adult tissues up to 12 mm. beyond the edge of the regenerate. The tissue dose was made uniform across the tissues by alternate positioning of the source on the two surfaces of the chamber. The specified dose has been determined by ionization measurements with a Victoreen chamber in a perspex phantom of the ear chamber. The dose rate was 16 roentgens per minute and the rabbit's ear was irradiated in air at constant temperature (70° F.) with the animal unanesthetized. A few of the earlier chambers were irradiated with roentgen rays (200 kv., half-value layer 1.3 mm. Cu, focal skin distance, 27 cm., field size 3.1 cm. in diameter, dose rate 45 roentgens per minute), but proved unsuitable for the delivery of single high doses, necessitating irradiation times of overlong duration for unanesthetized animals.

RESULTS

Unirradiated Chambers. In a series of normal ear chambers studied, lymphatics consistently regenerate if the tissue thickness is not less than 100 μ. With chambers of nonrigid construction which warp and give rise to chronic tissue tensions, vascular destruction and dense formation of fibrous tissue occurs, often resulting in failure of lymphatics to develop. The latter also applies to very thin chambers of less than 70 μ thickness and to the tantalum type chamber of Williams (Clark[8]).

However, quantitative estimations of the mean rate of growth of lymphatics are unsatisfactory. The mean rate of growth varies tremendously, the axis of growth for individual lymphatic buds changes continually, and the degree of fibrous tissue differentiation which takes place varies from place to place in the regenerate and greatly affects the ease with which lymphatics regenerate and survive (Clark and Clark[11,12]), (Fig. 1 and 2).

Effects of Irradiation on Regeneration.

1. With single doses below 1,000 gamma roentgens, a normal development of lymphatics occurs in the regenerate which forms after irradiation (Fig. 3 *a–e*).

2. With single doses of 1,000–2,000 gamma roentgens, lymphatics have been observed to regenerate after irradiation but much more irregularly, and usually growth ceases prematurely. Qualitatively, it has been noted that the lymphatic buds often have rounded tips with short solid cytoplasmic extensions which cannulate very slowly, and this has been correlated,

FIG. 1. Unirradiated ear chamber, (11L). Regenerating lymphatic buds (L) alongside small venules. Electronic flash photograph (×300).

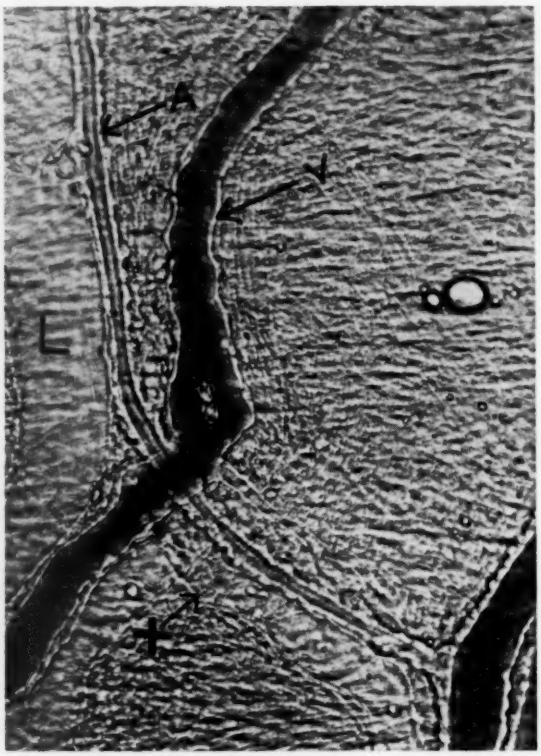

FIG. 2. Unirradiated ear chamber, (11L). Regenerated lymphatic vessels (L); arteriole (A); venule (V). At point X, fibrous tissue development is associated with "nipping" and early isolation of two segments of a lymphatic channel (×300).

with abnormal round cell infiltration of the tissues and increased fibrous development (Fig. 4 and 5). Sequestrated lymphatics are seen and the lymphatics are often dilated. Macrophages and leukocyte collections are frequently present in lymphatic tips, and although no "sticking" to the endothelial wall occurs, such collections may remain stationary for days, indicating a very sluggish flow (Fig. 5).

3. With doses of 2,000–4,000 gamma roentgens, lymphatic regeneration has not been observed, although lymphatics already formed prior to irradiation may persist (*vide infra*).

Lymphatic Regeneration in "Superregeneration." In regenerates which have been irradiated with doses in excess of 2,000 gamma roentgens causing cessation of vascular growth, further vascular growth can be induced by damaging the fibrous tissue "barrier" which forms in advance of the capillaries, giving rise to "superregeneration" (van den Brenk[30]). However, lymphatic regeneration has not been ob-

FIG. 3. Ear chamber (7RB) irradiated with single tissue dose of 1,500 gamma roentgens from Co^{60} source. Photographs taken of entire table area (×16). (*a*) One day preceding irradiation. Partial growth of the repair blastema has taken place. Residual unorganized clot in center. No lymphatics present. (*b*) Fourteen days following irradiation. Growth of the repair blastema now fills the chamber and a regenerated lymphatic system is present (L). (*c*) Nineteen days following irradiation. Further growth of lymphatic system. (*d*) Thirty-three days following irradiation. Second lymphatic system (L) now present. (*e*) Forty-five days following irradiation. Well developed lymphatic system serves tissues in chamber. (*f*) One hundred and fifteen days following irradiation. Wide dilatation of the lymphatic plexus (L) accompanies edema induced by loosening bolts holding cover on chamber and applying intermittent pressure.

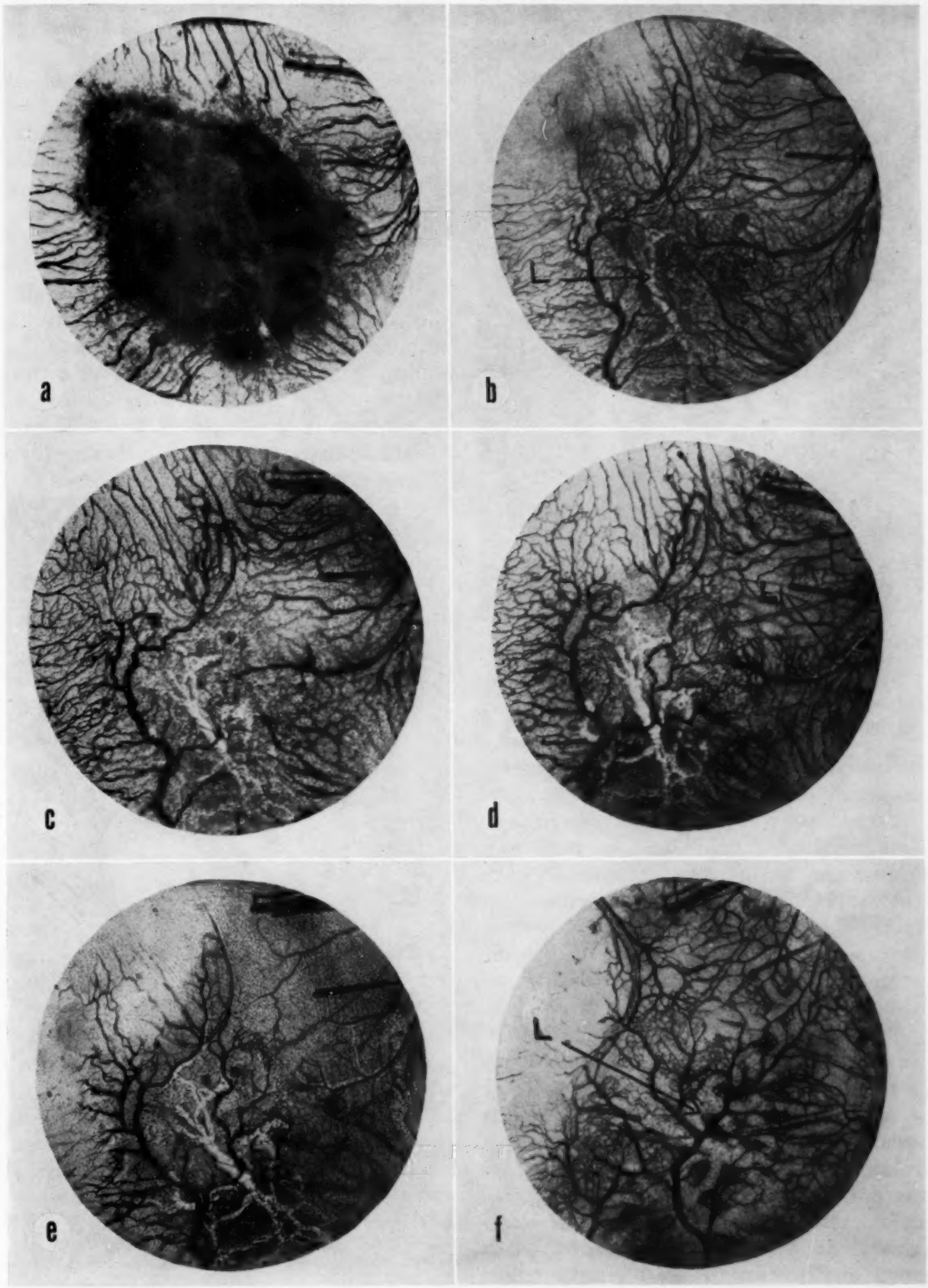
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FIG. 4. Ear chamber (7RB) irradiated with single tissue dose of 1,500 gamma roentgens. Dense round cell infiltration of tissues surrounding lymphatics impart a granular appearance to the lymphatics (L) (×40).

served as a concomitant of "superregeneration."

Irradiation of Preformed Lymphatics. The "inflammatory" reaction associated with irradiation damage, differs profoundly from the inflammation which accompanies certain other types of tissue damage (for example, pyogenic infections, turpentine abscess, etc.) in that proliferation of lymphatics fails to occur after irradiation (Fig. 7 *b-f*), although preformed lymphatics may dilate with the appearance of edema of the tissues (Fig. 3*f*). It is to be noted that the vascular proliferation which occurs in most inflammatory states, quite apart from vascular dilatation, also largely fails to take place after irradiation. Actually, there occurs a marked destruction of small blood vessels and lymphatic capillaries. With doses of the order of 4,000 gamma roentgens, larger lymphatics in preformed chambers survive, although finer lymphatics and blood capillaries suffer marked damage (Fig. 6 and 7).

Observations on lymphatics and blood capillaries in regenerated ear chambers have failed to show that significant endothelial swelling, that is increase in endothelial volume, occurs. This factor has not been found to cause significant narrowing of the lumen *per se*. If a lymphatic capillary degenerates after irradiation, rupture of the endothelial wall occurs, and the endothelium retracts and degenerates *in situ*—a situation comparable to the swelling of the wall of the hollow cylinder to form a constricted or solid tube has not been observed.

Infection in Irradiated Tissues. If pus extends onto the table in a regenerate which

FIG. 5. Ear chamber 7LB irradiated with single tissue dose of 2000 gamma roentgens. The tip of a regenerating lymphatic bud (L), contains a small clump of macrophages. An uncannulated growing extension (E) is present on extremity of bud. Surrounding tissues show pronounced round cell infiltration. Electronic flash photograph (×400).

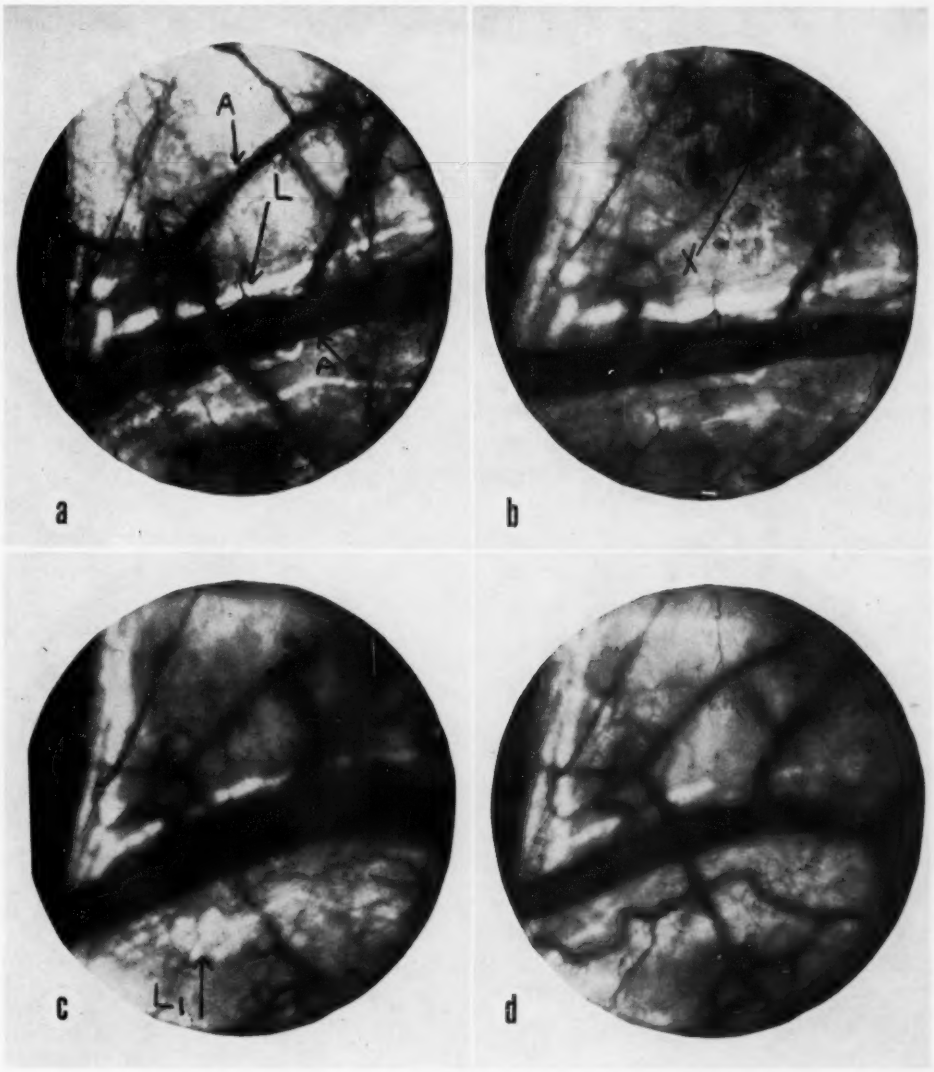
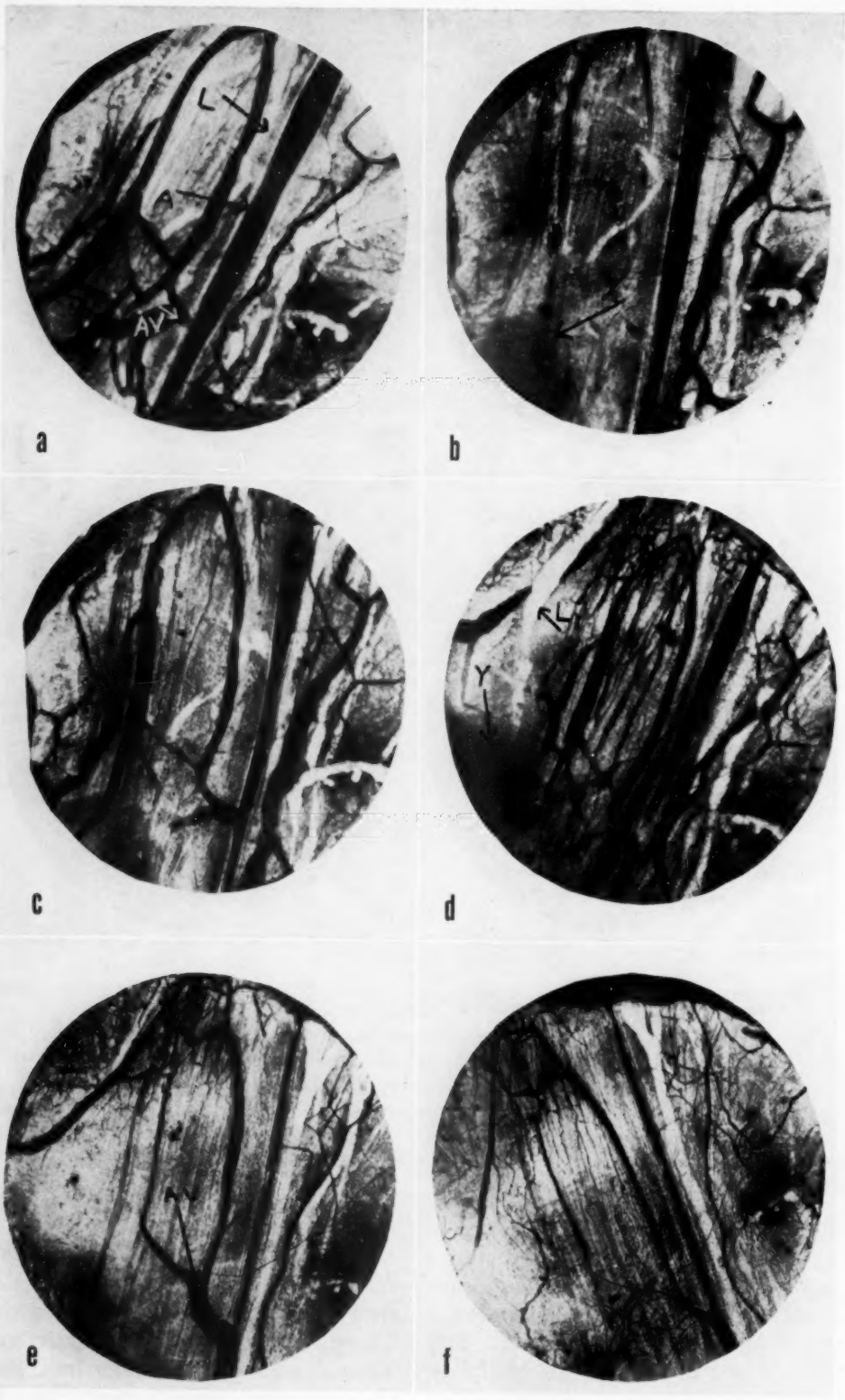


FIG. 6. Preformed ear chamber (14LX) irradiated with single tissue dose of 4,000 gamma roentgens (×15). (*a*) Immediately preceding irradiation. Small arteries (A) and lymphatics (L). (*b*) Twenty-four hours after irradiation. Marked destruction of small blood vessels with areas of hemorrhage and thrombosis (X), narrowing of arteries, and little change in caliber of main lymphatics. (*c*) Fourteen days after irradiation. Areas of hemorrhage have resolved. Slight dilatation of surviving vasculature and dilatation of smaller lymphatics (L_1). Marked round cell accumulation in tissues gives hazy picture and lack of clarity. (*d*) Three months after irradiation. Main lymphatics survive in tissue with little alteration. Patchy, abnormal vascular regeneration present, and vascular tone with due allowance for remodelling approaches normal.

has been irradiated previously with larger doses (2,000 gamma roentgens or more) while the preformed blood vessels and lymphatics may undergo dilatation, proliferation of lymphatics is not observed and vascular proliferation is also markedly reduced. Infection in such circumstances usually leads to complete necrosis of irradiated tissues (Fig. 7 *b–e*).

Effect of Certain Vasotropic Drugs on Irradiated Lymphatics. It has been found that unirradiated lymphatics in Sandison Clark ear chambers do not constrict with adrenalin nor pitressin, nor do other drugs so far tested (*vide supra*) influence the "tone" of the lymphatic system. Lymphat-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ics irradiated with 3,000 and 4,000 gamma roentgens, and exposed to the drug at various times after irradiation do not respond in any way differently from unirradiated lymphatics.

CONCLUSIONS

It is clear that ionizing radiations of the type used fail to stimulate lymphatic regeneration, but have an adverse effect on both the normal development of lymphatics in the repair blastema and on lymphatic proliferation which is the normal accompaniment to inflammatory conditions caused by certain pyogenic infections and chemical irritants.

While lymphatic regeneration has not been observed after doses in excess of 2,000 gamma roentgens, it does not necessarily follow that an intrinsic alteration in lymphatic endothelial cells has taken place which inhibits regeneration. It is highly probable that the excess development of fibrous tissue in the regenerate precludes the expression of a regenerative capacity which may still remain. This conclusion certainly applies to vascular regeneration. In the latter, recovery of regenerative powers by the vascular endothelium is shown not only by the slow type of "looping" which occurs into surviving, avascular fibrous tissue, but also by the phenomenon of "superregeneration" with normal vascular budding. The latter can be induced by a traumatic destruction of the fibrous tissue "barrier" (van den Brenk[30]) and vascular regeneration occurs at an undiminished rate.

The term radiosensitivity has been applied to the behavior of a cell type submitted to a spectrum of irradiation dosage of a given quality. One of the criteria of cell behavior which has been used in determining radiosensitivities is rate of growth. While such considerations may be valid and informative when applied to pure strain cells, *in vitro*, the growth behavior of a certain type of cell in a tissue complex subjected to irradiation *in vivo* provides less information on the inherent radiosensitivity of the cell. The differential qualitative changes induced in a tissue by irradiation bring about a state of affairs in which a given cell type may fail to grow, although no *intrinsic* reduction in growth capacity exists. The latter deduction is based on the phenomenon demonstrated for vascular tissues, that undiminished growth propensities may be elicited by artificial alterations in the cellular environment (van den Brenk[30]). Litschko[18] was the first worker to draw attention to the phenomenon of "superregeneration" in a study of limb regeneration after irradiation in axolotls.

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Fig. 7. Preformed ear chamber (77L) irradiated with single tissue dose of 3,000 gamma roentgens (×15). (*a*) Immediately preceding irradiation. Artery (A), lymphatics (L), arteriovenous anastomosis (AV). (*b*) Four days after irradiation. Purulent material due to small area of cartilage necrosis at edge of chamber has spread onto table at (X), causing local compression of vessels and lymphatics and some thrombosis. (*c*) Seven days after irradiation. Some absorption of purulent material at (X), partial vascular recovery but the typical hyperemic inflammatory response is poorly developed. Slight dilatation, but no proliferation of lymphatics. (*d*) Twenty-five days after irradiation. There is a mild generalized irradiation reaction present in chamber and some dilatation of lymphatics but no evidence of lymphatic proliferation, due to either the irradiation or the presence of tissue destruction and purulent material in chamber. A further extension of necrotic material at (Y) is accompanied by marked dilatation of related lymphatics (L_1). (*e*) Thirty-eight days after irradiation. The irradiation reaction has largely subsided, with considerable remodelling of the vascular pattern (note arteriovenous communication AV). The entire tissue has a reduced vasculature. The products of tissue destruction previously noted have been largely resorbed but in the absence of a typical "inflammatory" response and without vascular and lymphatic proliferation (see text). Larger residual lymphatics remain patent. (*f*) Sixty days after irradiation. A slow restoration of the vascular pattern has occurred, but there is no evidence of lymphatic proliferation although surviving larger lymphatics are present. The vascular pattern typifies irradiated connective tissues, with increased fibrosis and differs from the normal architecture associated with the dermis of the rabbit's ear (Cf. Figures 6 *a* and 7 *b*).

The dilatation of lymphatics in edematous states due to trauma and other damaging agents also takes place after irradiation. However, this phenomenon clearly must be distinguished from migration and proliferation of lymphatics. The latter, which readily occurs in pyogenic and chemical inflammations (Pullinger and Florey[24]), does not take place after irradiation and is seriously limited when irradiated tissues are subjected to infective and chemical agents.

It is suggested that although irradiation interferes with the intrinsic growth capacities of cells, this factor is not the essential issue which limits the normal tissue growth reactions to nonspecific tissue damage. The irradiated tissue is already qualitatively altered in such a way as to prevent the establishment of those regenerative mechanisms which depend on epimorphic growth in continuity from preformed cells which, intrinsically, still may be capable of such growth. The importance of inordinate development and maturation of fibrous tissue seems clear in the case of vascular and lymphatic regeneration.

The much quoted hypothesis of Borak[4] that endothelial swelling in vascular and lymphatic tissues occurs after irradiation and is of a magnitude which causes narrowing or blockage of lymphatics and capillaries has not been confirmed by *in vivo* studies and has no experimental foundation. It is suggested that while a cell may swell after irradiation, apparently due to protein breakdown products and increase in the intracellular osmotic pressure, for most tissues the increase in volume possible is limited. In endothelial tubes before the swelling reaches a magnitude sufficient to cause any observable mechanical blockage of the vessel lumen, a break occurs in the vessel wall or massive destruction *in situ* takes place. This explanation is certainly more consistent with the morphologic appearances observed *in vivo*.

SUMMARY

1. The behavior and regeneration of lymphatics following the administration of ionizing radiations from a Co^{60} source have been studied in the mammal using the *in vivo* technique provided by the Sandison-Clark type ear chamber in the rabbit.

2. Lymphatics have not been observed to regenerate in the repair blastema, following single doses in excess of 2,000 gamma roentgens. Single doses of 1,000 gamma roentgens permit a normal regeneration of lymphatics.

3. The phenomenon of "superregeneration" (Litschko,[18] van den Brenk[30]) in irradiated regenerates is discussed in connection with the regeneration of lymphatics.

4. Some of the effects of irradiation of a "preformed" lymphatic plexus are described. It has been shown that:

(a) Preformed lymphatics survive after doses of at least 4,000 gamma roentgens.

(b) Irradiation damage to tissues is not followed by intense lymphatic regeneration, as observed in many other damaging agents, *e.g.*, mechanical trauma, chemicals, infective agents.

(c) Bacterial infection or mechanical trauma in an irradiated tissue is accompanied by some dilatation of preformed lymphatics, apparently related to edema of the tissues, but regeneration of lymphatics has not been observed.

(d) Irradiation of lymphatic endothelium does not precipitate endothelial swelling of an order sufficient to cause blockage of the lumen, which is said to result in a regression of the lymphatic. Destruction of lymphatics is due to endothelial "rupture" and cellular disintegration.

(e) The reactions of irradiated preformed lymphatics to a series of vasotropic drugs have been studied, but no altered responses have been observed.

Cancer Institute Board
483 Little Lonsdale Street
Melbourne, Victoria, Australia

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THE EFFECT OF IRRADIATING THE EXTERIORIZED SMALL BOWEL ON SUGAR ABSORPTION*

By WILLIAM T. MOSS, M.D.
CHICAGO, ILLINOIS

WEIGHT loss and even cachexia during and subsequent to abdominal irradiation have been observed almost since the discovery of roentgen rays.[12,14] The radiation-induced physiologic changes responsible for this weight loss have never been clearly defined. Some of the known contributing factors include disturbances in gastrointestinal motility manifested as anorexia, vomiting, gastric retention and diarrhea, absorption changes in the small bowel[4,5,10] and probably remote changes in metabolism produced by circulating breakdown products of irradiated tissues.[9] The aim of this investigation was to define the significance of direct small bowel irradiation in the development of some of these functional disturbances. By studying post-irradiation changes in sugar absorption, the effects of irradiation on diffusion and phosphorylation can be evaluated. The absorption of glucose entails diffusion through a "membrane" as well as phosphorylation by epithelial cells. The absorption of L-arabinose entails diffusion only.

Both the "membrane" and the epithelial cells of the small bowel are altered morphologically by irradiation. Montagna and Wilson[11] have reviewed the epithelial changes after single total body irradiation with 550 to 1,000 r. The mitotically active cells of the crypts show a maximum destruction within forty-eight hours and re-epithelization of the crypts is complete within ninety-six hours. In contrast, the tips of the villi show a maximum cellular destruction in ninety-six hours and repair is not complete for several days. The cells on the tips of the villi originate as daughter cells from those of the crypts, and re-epithelization of the tips is dependent on a mitotically normal crypt epithelium. When the source of cells from the crypts is re-established, repair of the tips of the villi is rapidly completed. The subepithelial tissues show edema, capillary congestion, and degeneration of lymphoid tissues.

Motility and absorption disturbances accompany these morphologic changes. One of the earliest changes is a disturbance in gastric motility. A prolongation of gastric emptying time follows irradiation of almost any large volume of tissue even though the stomach is not included in the irradiated volume.[1,6,7,13] For this reason techniques devised to measure absorption changes alone must not depend on normal gastrointestinal motility. With this in mind Detrick *et al.*[4] measured glucose diffusion through excised segments of small bowel at various intervals after irradiation. Permeability declined sharply three to six days after 600 r total body irradiation. Detrick did not believe these changes could be correlated with degrees of cellular destruction though they would seem to correlate rather well with the data reported by Montagna and Wilson as cited above. Dickson[5] measured absorption of glucose from blind intestinal loops in the intact animal and reported maximal reduction in absorption rate seventy-two hours after 500 r total body irradiation. No similar studies of the effects of irradiation on exteriorized small bowel have been made.

MATERIAL AND METHOD

Male albino rats of the Sprague-Dawley strain weighing 120 to 180 gm. were used. After a forty-eight hour fast each animal was anesthetized with ether and the bowel exteriorized through a midabdominal incision. As indicated below, the bowel was irradiated, or shielded during total body

* From the Department of Radiology, Northwestern University, and the Veterans Administration Research Hospital, Chicago, Illinois.

irradiation, or in the control animals simply replaced in the abdomen. Irradiation was given with a 260 kv. peak Picker roentgen therapy machine, half-value layer 1.15 mm. Cu, filter 0.5 mm. Cu+1.0 mm. Al, target-skin distance 50 cm., 18 ma. The total dose varied with each group as shown below. Shielding was accomplished with lead plates 4.0 mm. thick. The abdomen was closed with silk.

Group I. Measurement of Gastric Retention Subsequent to 700 r to Exteriorized Small Bowel. At various intervals after irradiation as described above, 2 cc. of 50 per cent glucose was fed to the animal by stomach tube. Two hours later the animals were killed and the glucose remaining in the stomach was determined using the washing technique of Cori[3] and the quantitative sugar technique of Somogyi-Shaffer-Hartman.[8] Identical procedures including exteriorization of the small bowel were carried out on nonirradiated control animals (Fig. 1).

Group II. Glucose Absorption After 700 r to Exteriorized Small Bowel. Irradiated and nonirradiated controls were prepared as described above. At various intervals after irradiation or the sham operation in the control, the animal was again anesthetized, the abdomen reopened and the bowel ligated at the level of the pylorus and again at the terminal ileum. Two milliliters of 20 per cent glucose were injected into the lumen of the loop and the abdomen was again closed. One and one-half hours later, the animal was sacrificed and the sugar remaining in the small bowel was determined as outlined for Group I (Table I).

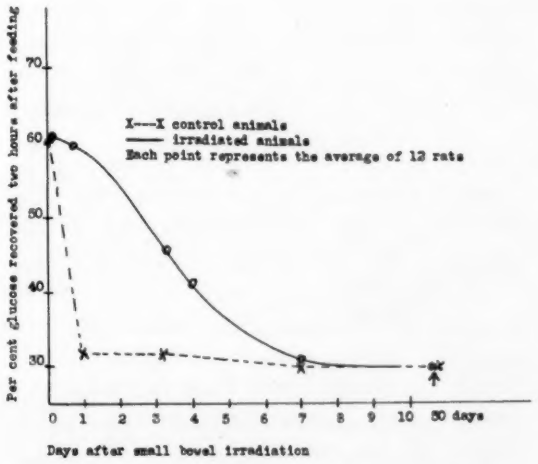
Per cent glucose recovered two hours after feeding
70
60
50
40
30
X---X control animals
—— irradiated animals
Each point represents the average of 12 rats
0 1 2 3 4 5 6 7 8 9 10 30 days
Days after small bowel irradiation

Fig. 1. Each point represents the average obtained of 12 rats. Graph showing variation in gastric emptying time following irradiation of the exteriorized small bowel. The initial prolongation of gastric emptying in the control animals indicates the effect of anesthesia and operation on this function.

Table I

GLUCOSE ABSORPTION SEVENTY-TWO HOURS AFTER 700 r TO EXTERIORIZED SMALL BOWEL

	No. Animals in Group	Ave. Per Cent Sugar Absorbed
Controls (no irradiation)	25	51.4
Irradiated (700 r to small bowel)	22	25.3

Group III. Glucose Absorption Seventy-two Hours after 2,000 r Total Body Irradiation, but with the Small Bowel Shielded. The exteriorized small bowel was shielded with 4.0 mm. lead during a single total body irradiation with 2,000 r. The abdomen was closed and the glucose absorption test as described in Group II was repeated seventy-two hours postirradiation. These animals were compared with the nonirradiated control group (Table II).

Group IV. Comparison of the Effectiveness of Irradiation in Inhibiting Glucose and Arabinose Absorption. The procedure

Table II

GLUCOSE ABSORPTION SEVENTY-TWO HOURS AFTER 2,000 r TOTAL BODY IRRADIATION BUT WITH SMALL BOWEL SHIELDED

	No. Animals in Group	Ave. Per Cent Sugar Absorbed
Controls (no irradiation)	25	51.4
Irradiated (2,000 r total body with bowel shielded)	11	52.5

TABLE III

COMPARISON OF THE EFFECTIVENESS OF IRRADIATION IN INHIBITING GLUCOSE AND ARABINOSE ABSORPTION (SEVENTY-TWO HOURS AFTER IRRADIATION)

		No. Animals in Group	Ave. Per Cent Sugar Absorbed
Glucose	Controls (no irradiation)	25	51.4
	Irradiated (700 r to small bowel)	22	25.3
Arabinose	Controls (no irradiation)	13	22.0
	Irradiated (700 r to small bowel)	15	13.1

given in Group II was repeated using a 16.4 per cent solution of L-arabinose (equal molarity to 20 per cent glucose) instead of 20 per cent glucose (Table III).

RESULTS AND DISCUSSION

As in irradiation of various other segments of the body, irradiation of the exteriorized small bowel produces prolongation of gastric emptying (Fig. 1). After 700 r this increases to a maximum quickly and returns to normal in eight days. The abnormality in the control animals must be a result of the anesthesia and operation. Swift and co-workers[13] have shown with other body tissues that the higher the dose, the more prolonged the effect. The mechanism of this remote effect of localized irradiation has not been defined, but it is suspected of being a consequence of radiation-induced tissue breakdown products being liberated in the blood. The failure to appreciate this delay in gastric emptying led Buchwald[2] to erroneous conclusions regarding changes in glucose absorption. Our control animals showed a very transient prolongation in gastric emptying resulting from the anesthesia and operation trauma.

Irradiation of the exteriorized small bowel with single doses of 700 r decreased the rate of glucose absorption strikingly (Table I). The fact that total body irradiation with small bowel shielding produced no significant change in absorption (Table II) indicates that the damage is directly on the bowel wall and not related to changes in blood sugar or injury to organs responsible for glucose metabolism.

Attempts to define the nature of this bowel injury were made in the Group IV animals. Dickson[5] could detect no quantitative change in hexokinase in irradiated intestines, but the method did not rule out the possibility of a radiation-induced suppression of phosphorylation. In Group IV animals, a physiologic measure of damage to phosphorylation was made by comparing the relative suppression of absorption of glucose and arabinose (Table III). Glucose absorption entails both diffusion and phosphorylation while arabinose absorption entails diffusion alone. The fact that arabinose abosrption is depressed less than glucose absorption suggests that damage to phosphorylation accounts for some of the change. However, the magnitude of the change in the absorption of both sugars suggests that a decrease in rate of diffusion is the major factor. The edema and vascular congestion could quite logically be expected to decrease the rate of diffusion.

SUMMARY

Irradiation of the exteriorized small bowel prolongs gastric emptying. It also decreases the rate of glucose and arabinose absorption from the small bowel but absorption of the glucose is influenced more severely. This suggests that phosphorylation is disturbed as well as the process of diffusion. However, the magnitude of the change in the absorption of both sugars suggests that a decrease in the rate of diffusion is the major factor.

Veterans Administration Research Hospital
333 East Huron Street
Chicago 11, Illinois

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ADDENDUM

In order to further define the effect of irradiation on phosphorylation, a fifth group of animals was studied. The method used was similar to that described by Barron *et al.*[15] However, instead of total body irradiation, the exteriorized small bowel alone was irradiated. Also, instead of using a gastric tube, the sugar was injected directly into the small bowel. The reasons for these changes were described above. Experimental and control animals were prepared as described under materials and methods. The experimental animals received 700 r to the exteriorized bowel; the control animals none. Twenty-four hours later 1.0 cc./30 gm. body weight of a 5 per cent glucose solution was injected directly into the bowel ligated as previously described. The animals were killed thirty-five to forty minutes later and using the method described by Beck,[16] organic phosphorus contents of the scraped off mucosal cells were determined. Values obtained on nonirradiated and irradiated animals were compared (Table IV).

TABLE IV

ORGANIC PHOSPHORUS CONTENT OF THE SMALL BOWEL MUCOSA TWENTY-FOUR HOURS AFTER 700 r IRRADIATION. ONE CC. OF 5 PER CENT GLUCOSE/30 GRAMS BODY WEIGHT WAS GIVEN THIRTY-FIVE MINUTES PRIOR TO SACRIFICE

	No. Rats	Mg. Organic Phosphorus Per 100 Mg. Dried Mucosa
Controls (no irradiation)	8	0.0947
700 r to exteriorized small bowel 24 hours before sacrifice	8	0.0568

Table IV illustrates the striking inhibition of phosphorylation produced by irradiation. Values were uniformly reduced to one-half by twenty-four hours after 700 r single dose. However, this finding does not alter the conclusions drawn above.

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STUDIES WITH A MODIFIED COLLIMATOR FOR USE WITH SCINTILLATION COUNTER FOR TOTAL BODY SCANNING*

By JOSEPH P. CONCANNON, M.D., *and* FRANCES BOLHUIS, R.T.
CHICAGO, ILLINOIS

THE major premise in the treatment of thyroid cancer with iodine 131 is to give it in therapeutic quantities to those patients who have tumor tissue which selectively acquires the radioiodine. It is necessary, therefore, to demonstrate that there is a concentration of iodine 131 in tumor tissue, so that therapy with this agent may be instituted without delay. A permanent record of iodine uptake is desirable so that comparisons of uptake can be made at a later date when tracer and therapeutic quantities are given.

External gamma ray counters are of the utmost importance in obtaining information concerning selective localization of radioiodine within the body. Although uncollimated or partially collimated gamma ray counters have been used for total body scanning, the resolution is so poor, that it is difficult to localize accurately a radioactive source, particularly when the source is at a considerable distance from the crystal. The principles involved in satisfactory collimation of gamma ray counters have been discussed by a number of authors.[1,5] It is hoped that with the use of collimated gamma ray counters detection of I^{131} localized in tumor tissue of thyroid origin will be facilitated and improved.

Scintillation counters with the conventional, commercially available, round collimators can readily detect localization of radioiodine in areas remote from the thyroid gland where a metastasis is known to exist. It is a much more complex problem with this equipment to discover functioning thyroid carcinoma deposits that are unsuspected clinically. Despite this difficulty, in a personally reported series of patients with thyroid carcinoma investigated with radioiodine at the Royal Marsden Hospital, London,[6] there were 2 patients in whom the total body scan gave the first indication that remote disease was present. In a third patient the scan not only demonstrated uptake in known metastases but also showed uptake in unsuspected ones. It is likewise difficult to detect functioning metastases adjacent to structures which normally contain radioiodine with this conventional type of collimator.

There is some disagreement among authorities as to the optimal time after ingestion of iodine 131 for external scanning.[10] Some believe that the patient should be scanned forty-eight hours later, so that the metastases of anaplastic thyroid carcinomas, which acquire but rapidly discharge radioiodine, will be detected. Others feel that total body scanning at seventy-two to ninety-six hours, when the body background is low, will result in the detection of metastases from well differentiated thyroid carcinomas, even if only small quantities of radioiodine are concentrated in thyroid cancer tissue. We decided to follow Pochin's example by scanning the body daily as long as there is appreciable evidence of I^{131} retention within the body,[3] beginning twenty-four hours after I^{131} drink.

Most methods and techniques for total body scanning in use today have limitations. The rounded, commercially available collimators "see" only relatively small areas. It is usual in doing a total body scan with this type of collimator, to scan along three or four parallel lines, determining the

* From the Department of Radiology, The Columbus Hospital, Chicago, Illinois. Presented at the Meeting of the Society of Nuclear Medicine, Salt Lake City, Utah, June, 1956.

counting rate at 5 cm. intervals along these lines. We found that it required two technicians working for two hours to complete a single body scan by this method. It usually required 20 "technician hours" to complete our routine scan, since we scanned the patient daily for at least five days. The records after five days of scanning were complex as well as bulky. It was obvious that we would have to reduce the time of daily scanning or scan at less frequent intervals.

Devices have already been described to shorten the time of total body scanning as well as to improve representation of radioactive distributions. Pochin uses a collimated G 10 lead Geiger-Müller tube, (cathode 8.5 cm. effective length). The change in long axis counting rate, with lateral shift of an I^{131} point source, is entirely accounted for by the inverse square law effect integrated over the effective length of the cathode.[2] A scanning rack carries the Geiger-Müller tube which may be moved mechanically or manually. However, the sensitivity of the Geiger-Müller tube is low, only ninety counts per minute per microcurie being recorded at a source in air-counter distance of 20 cm.

Mayneord[7,8] has described the use of a collimated coincidence scintillation counter driven mechanically, the gamma ray energy detected being converted into a light picture on a television screen, which may be photographed for a permanent record. Its clinical trial was described by Kramer, Concannon, Evans and Clark.[6] The cost of such a device and its maintenance, however, is prohibitive to the average general hospital.

A mechanically driven scintillation counter carrying a multichannel collimator has been described by Miller and Scofield.[9] Their scanning device carries the counter across the patient's short axis. Since only a small sector of the body is seen at any one scan, the graphic representation of distribution of radioactivity within the body becomes cumbersome.

It is the purpose of this paper to report the design of an inexpensive collimator which can be readily attached to conventional scintillation counters. This heavily shielded collimator when attached to a scintillation counter has a wide angle of "vision" laterally, which responds to the gamma rays of radioiodine from the whole width of the body. It has a narrow angle of "vision" at 90 degrees to the long axis and consequently has improved short axis resolution, as compared to the 4 cm. diameter circular collimators in general use. Although increased short axis resolution has been obtained, there has been only a 15 per cent loss of sensitivity at the same source-crystal distances. The time required to complete a total body scan with the counter-rectangular slit collimator combination has been reduced to a half hour daily. The scintillation counter with collimator is moved mechanically, and it is not essential that a technician be in the room during the entire time of examination. The record of the radioactivity detected within the body is in simple form and is readily comparable with later studies.

APPARATUS

The mechanical scanning rack (Fig. 1) consists of an aluminum channel supported at both ends by angle irons attached to a wooden table. The carriage is mounted on ball bearing wheels, which roll on two steel tracks inside the aluminum channel, and carries two vertical steel rods to which is attached the scintillation counter. These rods are perforated at centimeter intervals,

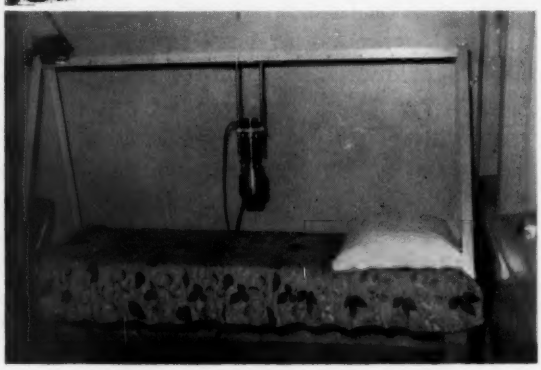

FIG. 1. Mechanical scanning rack with counter and rectangular slit collimator.

so that the height of the scintillation counter above the table top may be varied. The position of the face of the collimator may be varied from 10 to 33 cm. and the crystal from 21 to 44 cm. above the table top. The carriage is moved by a long lead screw which is motor driven through gearing. The inexpensive electric motor drives the counter from the head to the foot of the table at 4.4 cm. per minute at high speed and 2.2 cm. per minute when the low gear is engaged. An arm projecting from the carriage trips a switch at the end of the range of travel, stopping the electric motor. If desired the clutch may be disengaged and the counter moved by hand along the scanning rack.

The counter is connected through a linear amplifier to a rate meter and scaler in series. The linear amplifier is used to discriminate against all pulses below 300 kev. to reduce the counting rate due to the background and scatter radiation. The counting rate observed by the rate meter is recorded on paper for permanent record by a graphic ammeter. The scaler-rate meter circuit is easily interrupted and either scaler or rate meter may be used separately. The use of the scaler separately is considered to be important since it was found that with the rate meter it was difficult to choose a suitable scale such that the larger peaks would not be off the chart scale while the smaller peaks would be sufficiently distinct.

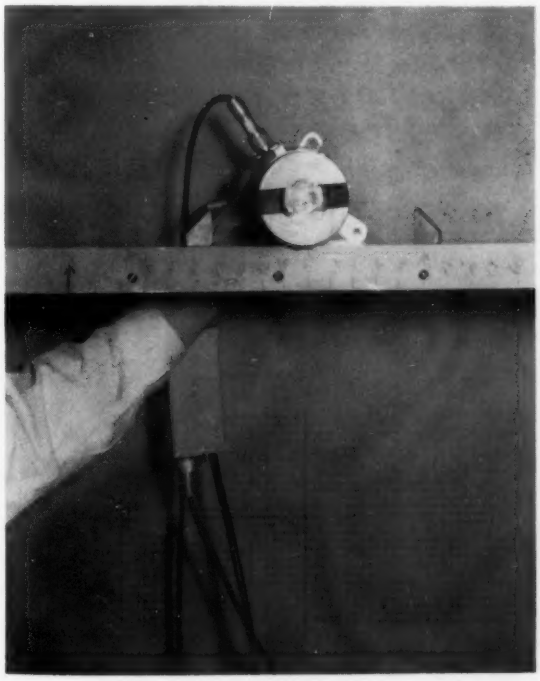

Fig. 2. Scintillation counter with segments of lead removed from either side of the crystal. The removed segments of lead are shown.

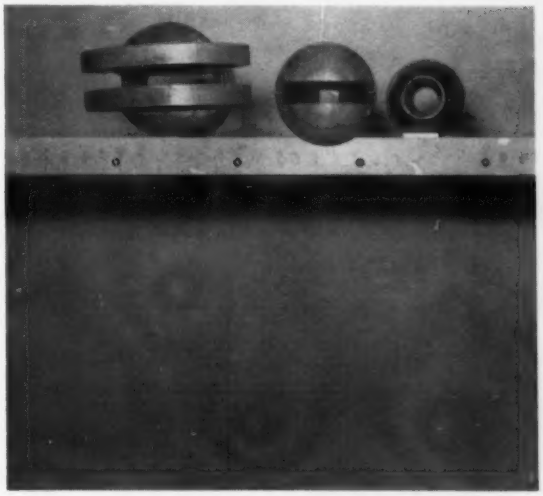

Fig. 3. Four centimeter circular collimator on the right, the pilot rectangular slit collimator in the middle, and the final rectangular slit collimator on the left.

Counts up to 100,000 per minute were recorded with the rate meter and scaler in series with a negligible error of 4 per cent. Two hundred thousand counts per minute were recorded with statistical accuracy when the linear amplifier, scaler circuit was used.

Although a conventional N. Wood laboratory scintillation counter with a pilot model collimator had improved ability to detect laterally placed sources, it was believed that this performance could be bettered. To further improve detection of laterally placed sources, segments of lead were removed from two sides of the crystal (Fig. 2), and an enlarged collimator (Fig. 3, 4 and 5) was designed with an extended slot covering a 90 degree angle of vision around the crystal. The segments of lead adjacent to the crystal, which were re-

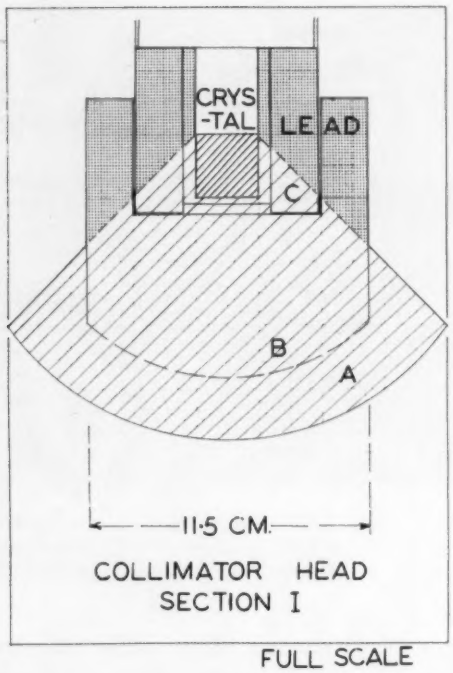

FIG. 4. Diagram through long axis of collimator. C indicates area from which lead was removed, B end of collimator as initially designed and A flanges that were later added to maintain short axis collimation when thick filters were used.

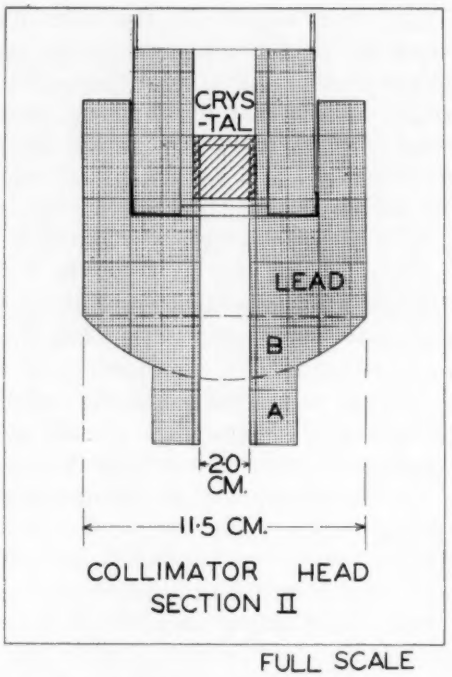

FIG. 5. Diagram 90 degrees to long axis of collimator.

moved, can be replaced so that more finely collimated studies can be done when collimators with smaller apertures are used.

The collimator as designed was not completely satisfactory since there was decreased short axis resolution when increasing thicknesses of lead filtration were used. Short axis resolution became independent of filter thickness only after lead flanges 2.0 cm. wide and 3.0 cm. in height were added to each side of the collimator slot. The final collimator with flanges weighs 31 pounds. Table 1 illustrates the short axis resolution of the collimator with and without flanges. As the ratio of the filter width to the thickness of the collimator without flanges approached unity, there was increased percentage transmission of photons through that portion of the collimator adjacent to the filter.

PHYSICAL STUDIES

A comparative study was made using the rectangular slit collimator and the 4 cm. round collimator. The counting rate, due to a radioiodine point source in a water phantom and in air, was determined at the center and at points lateral to the center of the collimators at various source-crystal distances. Segments of lead were removed from the built in lead protection around the crystal for the studies done with the rectangular slit collimator. These lead segments were returned to their proper position adjacent to the crystal for the studies done with the round collimator.

TABLE I

SHORT AXIS WIDTH AT HALF HEIGHT IN CENTIMETERS

Filter No.	Collimator without Flanges	Collimator with Flanges
0	2.0	2.0
1	2.0	2.0
2	2.7	2.0
3	2.8	2.0
4	3.0	2.0
7	4.0	2.0
8	4.2	2.0

The long and short axis studies of the rectangular slit collimator are compared with studies of the round collimator in only one plane since the isometric curves of the round collimator are symmetrical in all planes.

Figure 6 represents half the isometric curve in the long axis of the rectangular slit collimator obtained from an I^{131} point source in a water phantom at a water surface-crystal distance of 20 cm., the radioactive source being progressively moved deeper in the water. The width at half height on the surface of the water phantom is 38 cm. and the width at half height widens as the source is moved deeper in water as is shown by the dotted line. This width at half height in the long axis of the rectangular collimator was reduced by 30 per cent when the lead segments were not removed from their position adjacent to the crystal.

Similar studies with a 4 cm. diameter round collimator at the same crystal-water surface distance showed the width at half height at the surface of the water phantom to be only 10 cm. Figure 7 illustrates the increase in lateral "vision" of the rectangular collimator in relation to that of the round collimator at varying source-crystal distances.

A set of eight lead filters was made to provide a broad range of sensitivities so that patients could be scanned after the administration of therapeutic as well as large tracer quantities of radio-iodine (Table II).

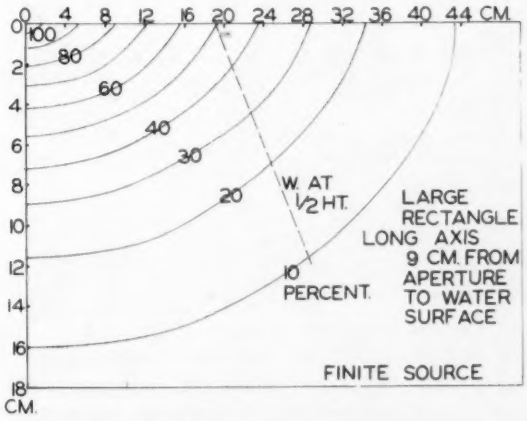

Fig. 6. Isometric lines of response of the rectangular slit collimator to an I^{131} point source in a water phantom. Dotted line indicates increasing width at half height as source is moved at progressively greater depths.

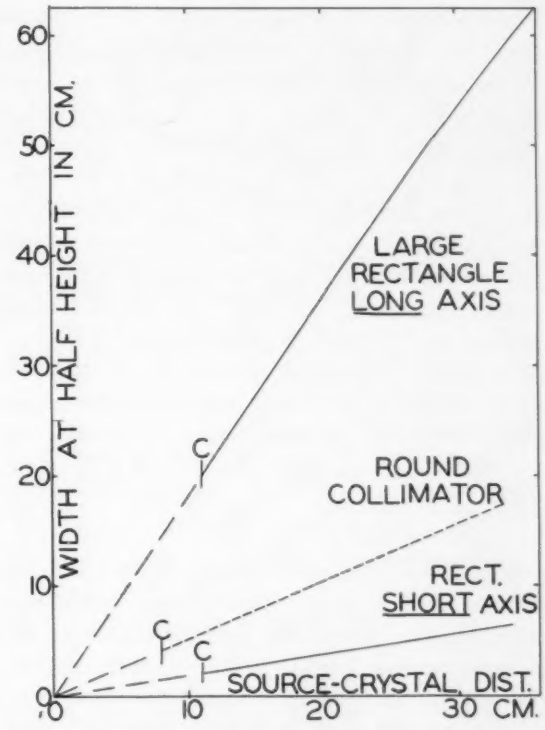

Fig. 7. Width at half height for rectangular slit collimator in long and short axis compared with that of the round collimator at various source-crystal distances.

It was considered that the long axis isometric curves obtained through these filters could be flattened by wedging the filters. A wedge filter is an absorber of unequal thicknesses so that a desired percentage transmission of photons at various points can be achieved. The use of wedge filters in roentgen therapy had first been described by Ellis and Miller[4] in 1944 and elaborated upon by a number of authors since. The purpose, design and performance of the rectangular slit collimator lent itself admirably to the application of the wedge filter principle.

The problem in the design of these wedge filters was simplified here by the use of a pulse height discriminator so that complications due to scatter radiation were

TABLE II

COUNTING RATE COUNTER—RECTANGULAR COLLIMATOR COMBINATION WITH FILTERS

Wedge Filter No.	Counting Rate Per Cent	13 Cm. Source-Crystal Distance		20 Cm. Source-Crystal Distance-Air	
		cpm/μc	μc for 100,000 cpm	cpm/μc	μc for 100,000 cpm
0	100.0	1,570.0	64.0	660.0	151
1	37.0	580.0	172.0	244.0	410
2	13.6	214.0	467.0	90.0	1,110
3	6.8	107.0	935.0	45.0	2,220
4	2.66	41.7	2,400.0	17.5	5,700
5	1.27	20.0	5,000.0	8.3	12,000
6	0.67	10.5	9,500.0	4.4	22,600
7	0.39	6.2	16,100.0	2.6	38,400
8	0.25	3.92	25,600.0	1.7	59,000

avoided. At a known radioactive source to crystal distance, the percentage counting rate without filtration was determined at several points lateral to the center of the rectangular collimator until the position of the 50 per cent counting rate was determined. Since the length of the filters was 17 cm., the proportion between filter length and width at half height, determined without filtration, was seen to be 0.43 (Fig. 8). The filter thickness was reduced from 100 per cent in midline to 50 per cent at the edge, the graduation in thickness of the filter being proportional to the percentage transmission of photons before wedging.

Although all filters were designed on the same principle, there were small insignificant variations in the isometric curves obtained with different filters. Figure 9 is a long axis isometric curve obtained through a lead filter and Figure 10 is a long axis resolution curve comparing the performance of the round collimator with performances of the rectangular collimator with and without wedge filters.

The short axis resolution of the rectangular collimator showed a considerable improvement when compared with the resolution obtained with the 4 cm. diameter rounded collimator. Figure 7 compares the short axis resolution of the two collimators at various source-crystal distances. It is seen that even at the shortest source-

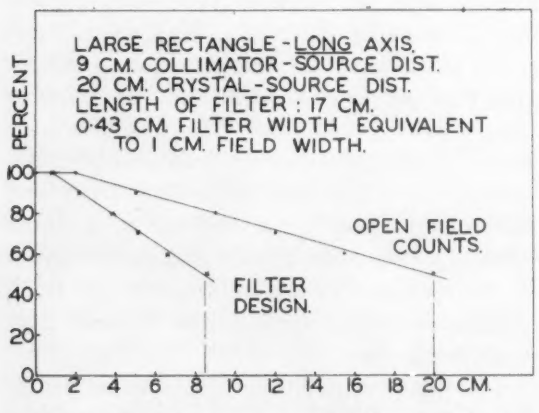

FIG. 8. Graphic representation of wedge filter design.

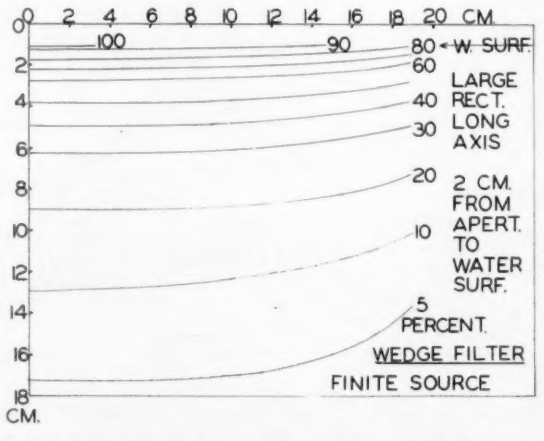

FIG. 9. Isometric curve obtained with counter-rectangular slit collimator with a wedge filter.

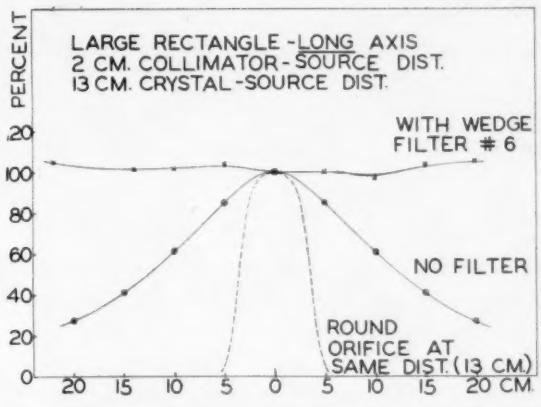

FIG. 10. Lateral response curve of the rectangular slit collimator in long axis with and without wedge filter, and round collimator at same crystal-source distance.

crystal distance there is an improvement of 2.7:1 in short axis resolution for the rectangular collimator.

This improved short axis resolution is important in discriminating between two sources of radioactivity adjacent to each other. Inability to discriminate between two sources may result in inability to discriminate between two adjacent functioning metastases or between a functioning metastasis and an adjacent anatomic structure which normally accumulates radioiodine.

It was found that a 4 cm. separation between two point sources was the minimum separation necessary to produce two separate and distinct peaks when the face of the rectangular slit collimator was 2 cm. away from the radioactive sources (Fig. 11). The round collimator at this same collimator-source distance was unable to distinguish between the two sources; a separation of 7 cm. was necessary to produce similar

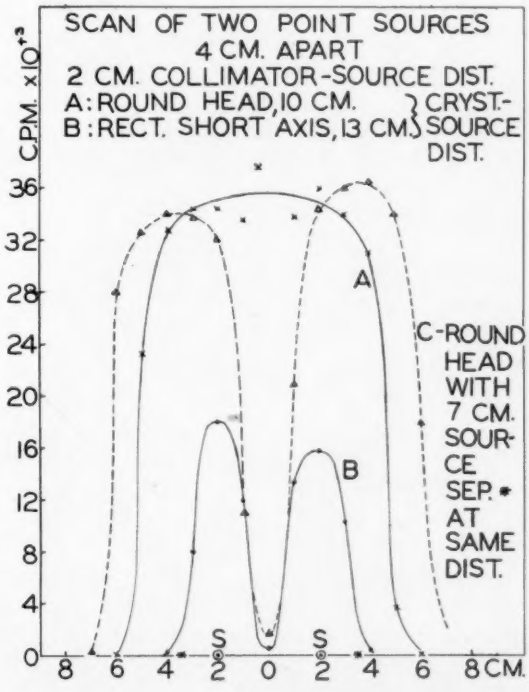

FIG. 11. Scan of two point sources. A 4 cm. separation between two point sources is necessary to produce two separate and distinct peaks when the face of the rectangular slit collimator is 2 cm. away from the radioactive source. A 7 cm. separation is necessary to produce similar distinguishing peaks when the round collimator is used at the same collimator-source distance.

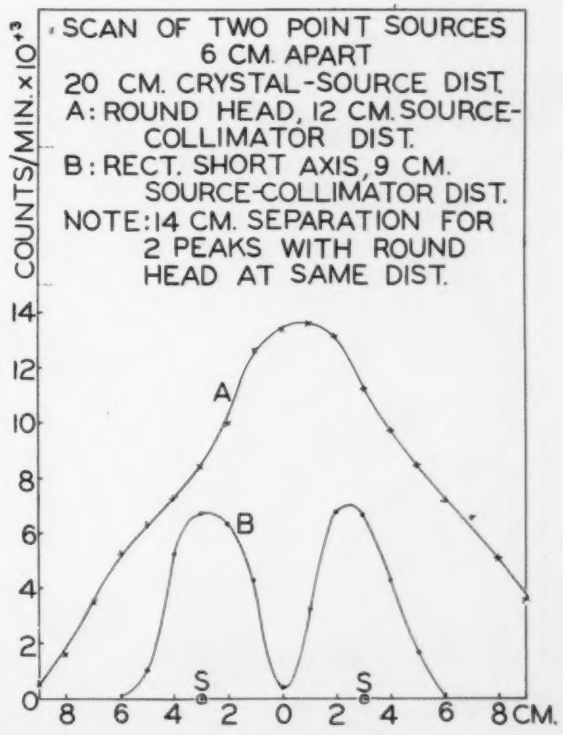

FIG. 12. Scan of two point sources at increased collimator-source distance. A 6 cm. separation between two radioactive sources is necessary to produce two peaks with the rectangular collimator. A 14 cm. separation is necessary with the round collimator to produce the same effect.

distinguishing peaks. This relative inability of the round collimator to distinguish between adjacent sources was magnified at increased source-collimator distance. Figure 12 shows that a 6 cm. separation between two radioactive sources is necessary to produce two peaks with the rectangular collimator, while a separation of 14 cm. is necessary with the round collimator to produce the same effect.

These studies showed that there was a steep fall-off in percentage counting rate as the source was progressively moved deeper in the water phantom. Since this fall in percentage counting rate could lead to failure to detect a metastasis deep within the body, we now scan posteriorly as well as anteriorly. Anticipating a future development, it was considered possible to have opposing scintillation counters, in parallel with rectangular collimators, moving and registering synchronously. Figure 13 is a composite short axis isometric curve which might be expected with such an arrangement of counters and collimating systems.

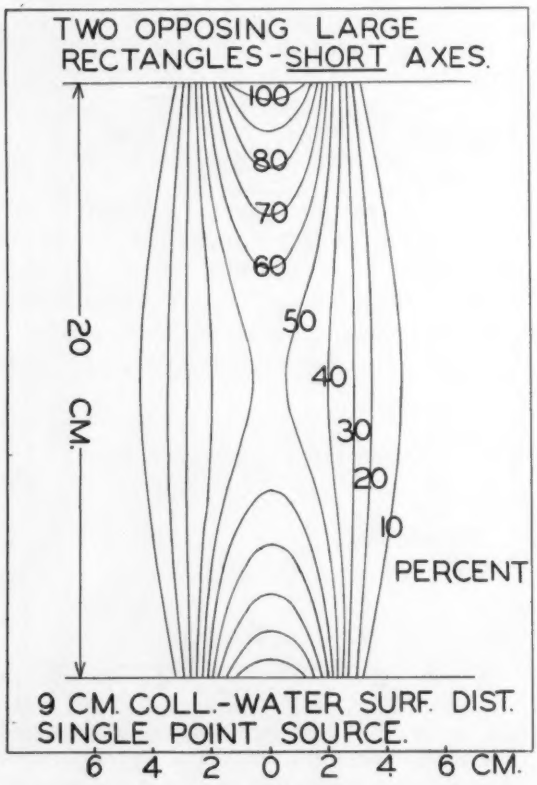

Fig. 13. Composite isometric curve expected to be obtained with two opposing counters with rectangular slit collimators.

SUMMARY

1. An inexpensive mechanical rack and rectangular slit collimator for total body scanning which is adaptable to conventional scintillation counters has been described.

2. This rectangular slit collimator has approximately a 4:1 improvement in detection of laterally placed I^{131} sources.

3. It has an improved short axis resolution of nearly 3:1.

4. These improvements have been obtained with only 15 per cent loss of sensitivity at the same crystal to radioactive source distance.

5. The design and the use of wedge filters have been described.

6. A future use of opposing scintillation counters has been described.

Joseph P. Concannon, M.D.
Department of Radiation Therapy
Jefferson Medical College
1025 Walnut Street
Philadelphia, Pennsylvania

I am deeply indebted to Dr. Pochin, Director of the Department of Clinical Research, University College Hospital, London, for my introduction in 1953 to his method of "profile scanning." Mr. R. Dvorak aided in the development of the collimator and Dr. W. A. Jennings gave much valuable advice. Mrs. Jean Walsh typed the manuscript.

ADDENDUM

Since completing this work, it has been brought to our attention that the concept of a rectangular slit collimator for scintillation counting has been explored by Jensen and Larsson of Scandinavia. The Scandinavian system does not include removal of lead adjacent to the crystal, wedge filters, or the concept of simultaneous scanning with opposing counters. The width at half height obtained with their collimator-scintillation counter combination is 35 per

cent less than that obtained with the one described in this paper.[11]

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EXTERNAL IRRADIATION OF THE THYROID GLAND IN DOGS

EFFECTS OF LARGE DOSES OF ROENTGEN RAYS UPON HISTOLOGIC STRUCTURE AND I^{131} METABOLISM*

By PAUL M. ST. AUBIN,† RALPH M. KNISELEY,‡ *and* GOULD A. ANDREWS
OAK RIDGE, TENNESSEE

WITHIN a period of a few days following internal irradiation of the thyroid gland by the administration of large doses of I^{131} both in human beings[1-4] and in normal dogs,[5] drastic changes in thyroid structure and function appear. Associated with the loss of colloid from the follicles of the gland, and hemorrhagic changes within the gland, a sharp secondary rise is noted in the plasma I^{131}. Smaller doses of internally administered radioisotopes I^{130} and I^{131} [3] and external beam ionizing radiation have been well shown to produce depression of thyroid activity in hyperthyroidism.[8] The normal thyroid gland, on the other hand, appears to be relatively resistant to the effects of externally administered ionizing radiation even with doses far exceeding those used in the treatment of hyperthyroidism. In the cases reviewed by Lindsay *et al.*,[6] for example, little alteration in function, and variable minimal changes in histologic structure were noted following external beam therapy with roentgen rays or radium in cases of laryngeal carcinoma where the thyroid gland is of necessity included in the field. This radioresistance of the thyroid gland is also shown in the experimental work of Walters, Anson, and Ivy,[10] and Bower and Clark.[2]

In view of the apparent natural resistance of the normal thyroid gland to ionizing radiation, and the remarkable effect of large doses of I^{131} on function and morphology of this gland, a study was made to see whether similar results would occur following very large doses of externally administered roentgen radiation. Thyroid function was evaluated by means of tracer doses of I^{131} with measurements of the plasma levels and the percentage of the administered dose concentrated in the gland. Microscopic changes were studied, and I^{131} distribution in the gland was determined by autoradiography.

MATERIALS AND PROCEDURE

Dogs were chosen as the experimental animal in order to compare results with the previous study of Levene, *et al.*,[5] and because of the relatively easy localization of the thyroid gland by means of external surface markings. Twenty-three dogs weighing from 10 to 26 kg. were given an intravenous tracer dose of carrier-free I^{131} of 5 μc per kg. The animals were not selected for age or sex and were not given a special diet. They were kept in individual cages up to the time of sacrifice. Daily samples of venous blood were collected in syringes containing small amounts of heparin, and radioactivity measurements were made at a distance of 15 cm. over the region of thyroid gland, liver, and right thigh with a collimated scintillation counter. The thigh counts were used as body background. The radioisotope present in the thyroid gland was expressed as a percentage of the original dose administered, by comparing the net count over the thyroid gland with a count obtained at the same distance over a simulated dog thyroid gland standard containing an aliquot of the original tracer I^{131} dose.

* From the Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee, under contract with the United States Atomic Energy Commission.

† Work done while a postresident in radiology at the Medical Division. Present address: Department of Radiolgy, Massachusetts General Hospital, Boston, Massachusetts.

‡ Present address: Department of Pathology, Eden Hospital, Castro Valley, California.

Whole plasma and plasma proteins separated by precipitation with 20 per cent trichloracetic acid were assayed in a scintillation well counter standardized for I^{131}.

Forty-eight hours after the administration of the I^{131} tracer, with the animal under nembutal anesthesia, a single dose of external roentgen rays was administered to the thyroid gland by means of a 250 kv. machine at 15 ma., with a filtration of 0.5 mm. Cu, 1 mm. Al. The half-value layer of this beam was 1.3 mm. Cu. The output of the machine at the treatment distance of 28 cm. and field size of 4 by 6 cm. was 300 r/minute. An estimated dose of 10,500 r (30,000 gram roentgens) and 21,000 r (60,000 gram roentgens) was delivered to the thyroid gland in thirty-five and seventy minutes, respectively. For the period of treatment the integral dose in gram roentgens was calculated according to the method of Mayneord.[7]

Nine of the earlier dogs so treated were operated on in an effort to spare radiation damage to the skin. This procedure was carried out with nembutal anesthesia under aseptic conditions and consisted of a midline neck incision with a separation of the skin and subcutaneous tissue from the underlying fascia of the neck. The skin was then held back with towel clips to expose the strap muscles overlying the upper trachea through an opening 8 by 10 cm. A number of controls were operated upon in this manner, but were not treated with roentgen rays. This was done to determine

Table I

SUMMARY CHART

Dog No.	Dog Weight, Kg.	I^{131} Dose, μc	Interval to Sacrifice or Death (days)	Essential Histologic Change
Roentgen-ray Dose to Thyroid Gland 21,000 r				
322	10.2	51.0	2	None
320	10.8	54.0	3	Early degeneration
321	19.4	97.0	5	Early degeneration
311	12.5	62.5	7	Patchy degeneration
312	20.0	100.5	7	Advanced destruction
316	11.3	56.5	7	Advanced destruction
314	19.0	103.5	8	Necrosis*
317	10.0	50.0	8	Advanced destruction
324	16.7	83.5	9	Advanced destruction
309	26.0	130.0	10	Hemorrhagic necrosis*
307	21.4	130.5	13	Hemorrhagic necrosis
323	12.4	62.0	14	Hemorrhagic necrosis
Roentgen-ray Dose to Thyroid Gland 10,500 r				
319	16.0	80.0	8	Early degeneration
318	14.7	73.5	31	Patchy degeneration
Nonirradiated Controls				
308	19.7	82.5	0	None
310	15.0	75.0	10	None
313	16.0	87.0	13	None
325	9.6	48.0	24	None
326	12.3	61.5	24	None
327	14.3	71.5	24	None

* Postmortem change prevented detailed histologic study.

whether the operation alone would influence the metabolism of a tracer dose of radioiodine. As a result of infection complicating the operative procedure, and aggravating the severe radiation reaction to the neck tissues, the operative procedure was discontinued, and external irradiation was carried out on the remaining dogs through an intact skin portal. Evaluation of the data indicated that if there were any effects of the operation or its complications on thyroid function, they were slight compared with the effects of the external irradiation. Consequently, all dogs were grouped in the three categories depending on the roentgen-ray dose and without regard for the surgical procedure.

In the dog, the thyroid gland consists of two unconnected ovoid lobes separated by the trachea and located 2 to 3 cm. caudal to the level of the laryngeal eminence. In order to ensure that both lobes of the thyroid were in the central region of the field of treatment, a neck roentgenogram was made before and after each treatment while the animal was in position.

Table 1 summarizes the pertinent data on all the dogs studied. After intervals of two, three, five, seven, eight, nine, ten, thirteen, and fourteen days, one or more dogs of the 21,000 r (60,000 gr.) group were sacrificed or died as the result of the procedure. The 10,500 r (30,000 gr.) dogs were sacrificed at the end of eight and thirty-one days.

Sacrifice was carried out by bleeding under anesthesia. At postmortem ex-

TABLE II

AVERAGE VALUES WITH STANDARD DEVIATION FOR DOGS TREATED WITH 21,000 r

Day	Thyroid I^{131} Content (Per cent of Dose)		Plasma I^{131} ($\mu c \times 10^{-4}$/ml.)		Plasma Protein Bound I^{131} ($\mu c \times 10^{-4}$/ml.)	
	Treated	Control	Treated	Control	Treated	Control
−1	25±11 (11)	20±11 (6)	41.8±12.9 (12)	34.3±17.8 (6)	2.4±1.0 (9)	1.8±1.4 (4)
0	26±13 (12)	27± 7 (6)	19.2±11.1 (12)	15.2± 7.4 (6)	2.3±0.5 (11)	1.8±0.9 (6)
1	33±10 (12)	30± 2 (5)	10.5± 6.7 (12)	6.9± 3.9 (5)	1.9±0.9 (12)	1.7±0.4 (5)
2	30± 9 (12)	30± 2 (5)	7.5± 4.5 (12)	4.6± 2.4 (5)	1.9±0.5 (12)	2.0±1.0 (5)
3	28±10 (11)	28± 3 (5)	6.5± 3.7 (11)	3.6± 1.1 (5)	2.1±0.6 (11)	2.1±0.6 (5)
4	26±10 (10)	30± 1 (5)	6.5± 2.5 (10)	3.5± 1.5 (5)	3.0±1.6 (10)	1.9±0.8 (5)
5	23±12 (10)	33± 7 (5)	9.4± 5.2 (10)	2.9± 0.7 (5)	5.0±3.7 (10)	2.0±0.5 (5)
6	19±10 (9)	29± 3 (5)	11.7± 7.1 (9)	3.2± 0.4 (4)	7.1±5.3 (9)	2.2±0.5 (4)
7	16±11 (8)	27± 2 (5)	17.8±11.4 (8)	2.6± 0.5 (5)	11.1±7.3 (8)	1.7±0.5 (5)
8	9± 5 (4)	27± 3 (5)	13.3±10.5 (4)	2.5± 0.6 (5)	7.3±4.7 (4)	1.7±0.6 (5)
9	7 (3)	26± 4 (5)	12.9 (3)	2.4± 0.8 (5)	6.1 (3)	1.8±1.1 (5)
10	5 (2)	24± 4 (5)	10.2 (2)	2.4± 0.6 (5)	5.0 (2)	1.9±0.4 (5)
11	4 (2)	26± 2 (4)	9.3 (2)	2.2± 0.6 (4)	3.1 (2)	1.5±0.6 (4)
12	2 (2)	23± 4 (4)	9.4 (2)	2.1± 0.2 (4)	3.5 (2)	1.6±0.4 (4)
13	1 (2)	22± 3 (4)	9.7 (2)	1.9± 0.4 (4)	3.2 (2)	1.1 (3)
14		21 (3)		2.0 (3)		1.3 (3)
15		21 (3)		1.8 (3)		1.5 (3)
16		19 (3)		1.9 (3)		1.5 (3)
17		18 (3)		2.1 (3)		1.2 (3)
18		19 (3)		1.6 (3)		1.8 (3)
19		17 (3)		1.1 (3)		1.5 (3)
20		17 (3)		1.2 (3)		1.5 (3)
21		17 (3)		2.1 (3)		1.8 (3)
22		15 (3)		2.6 (2)		1.3 (3)
23				2.6 (1)		1.8 (1)

Note: Number of animals in parentheses.

amination the thyroid glands were weighed and prepared for histologic studies and autoradiography.

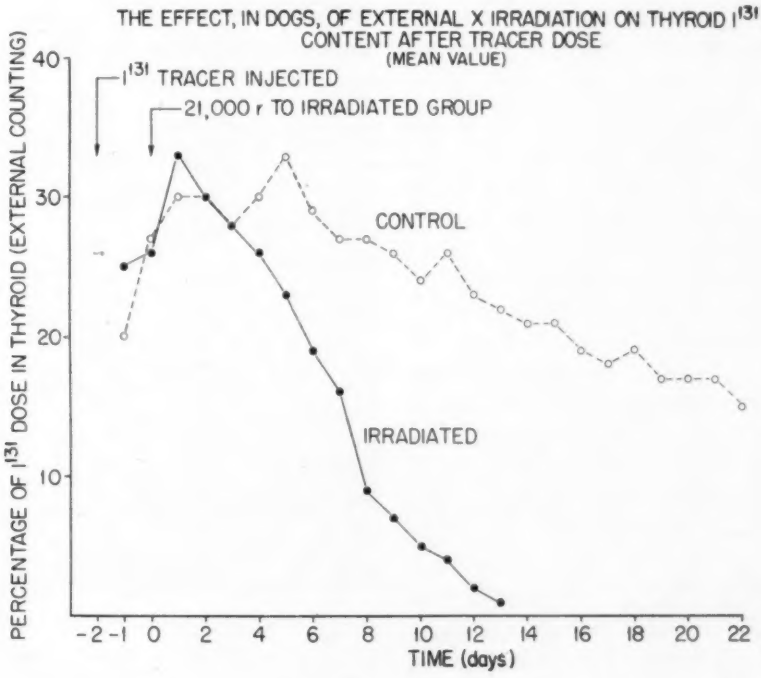
RESULTS

Clinical Changes. All irradiated animals in the 21,000 r (60,000 gr.) group had loss of appetite, skin erythema after twenty-four hours, and swelling of the neck. When vomiting developed, the animals normally did not live more than two or three days. Ulceration of the skin did not develop in the nonoperated animals; those operated upon showed infection and failure of healing. Narcotics were given to some dogs that appeared to be in distress. There was no generalized bleeding and no evidence of respiratory obstruction. The exact mechanism of death was not apparent.

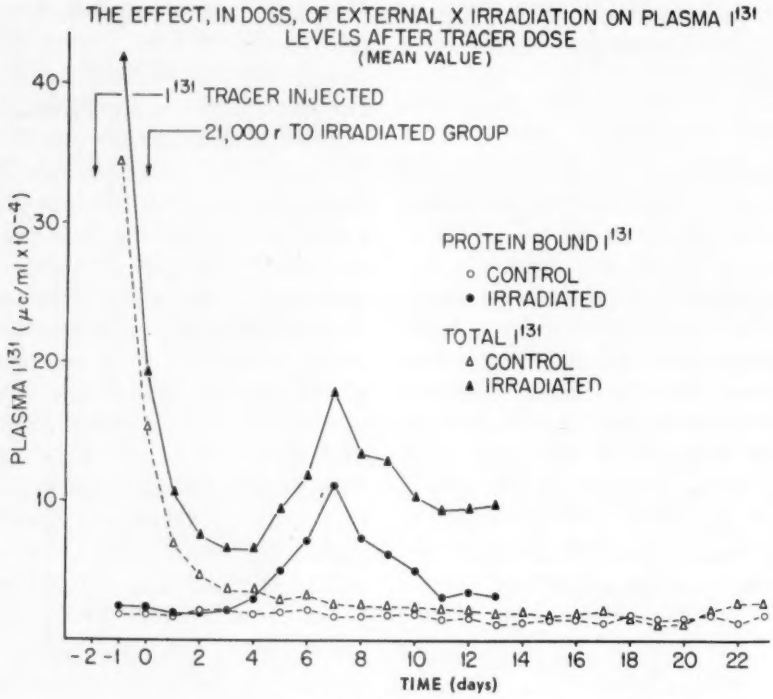
Radioactive Counting Observations. Table II shows the percentage of I^{131} dose in the thyroid, the total plasma I^{131}, and the protein bound plasma I^{131} in the dogs given 21,000 r. Standard deviations are given for the groups with 4 or more animals. Graphs I and II are based upon the same data.

For the 2 animals given 10,500 r, all of the information is shown on Graph III, and numerical data are omitted.

Pathologic Changes. (*a*) Nonirradiated Dogs. In the control animals the thyroid lobes, which averaged 1.2 gm. per pair, were pale pink-tan with glistening surfaces and were moderately firm in consistency. The histologic variations were somewhat more prominent than was expected. Each gland showed areas that were considered abnormal, with follicles that were devoid of colloid or that had pale-staining colloid. These appeared sometimes isolated in normal areas but usually were grouped together in irregular zones which often had a diameter the size of a low-powered field. In addition to lack of colloid, there was, in these zones, a tendency for follicles to be small and there were also areas of solid epithelial tissue, apparently nonfollicular in arrangement. Associated with the lack of colloid was the presence, in some instances,


THE EFFECT, IN DOGS, OF EXTERNAL X IRRADIATION ON THYROID I131 CONTENT AFTER TRACER DOSE
(MEAN VALUE)
I131 TRACER INJECTED
21,000 r TO IRRADIATED GROUP
CONTROL
IRRADIATED
PERCENTAGE OF I131 DOSE IN THYROID (EXTERNAL COUNTING)
40
30
20
10
-2 -1 0 2 4 6 8 10 12 14 16 18 20 22
TIME (days)

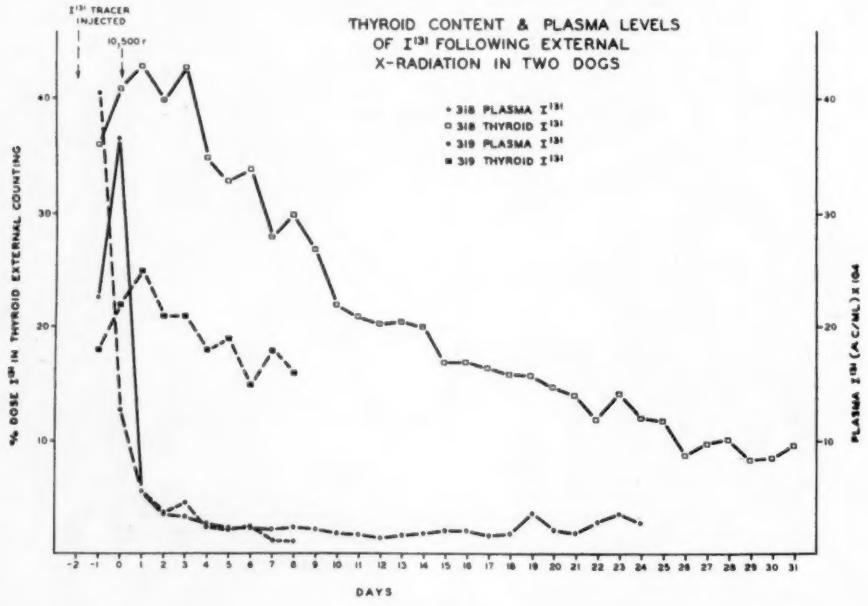
Graph I



GRAPH II

of groups of free cells in the centers of follicles. Some of these were thought to be epithelial cells, broken away from the follicle rim and showing nuclear pyknosis; others were phagocytes not containing colloid.

We were not certain that these features in untreated animals were truly abnormal,



GRAPH III

but they were somewhat disturbing and made interpretation of early radiation effects in treated animals difficult. Possibly the nonuniformity of these animals in age, sex, and nutrition explains these features, but it was notable that fibrosis was not prominent and that the variations were in the epithelial tissue.

(*b*) Dogs Receiving 21,000 r. Grossly the appearance of the thyroid lobes at the two-day and three-day intervals was not remarkable. Microscopically, the general architecture was intact without necrosis or hemorrhage. However, even at two days there were areas where the follicles were small and contained numerous phagocytes. Some of the colloid was granular; no phagocytosis of colloid was observed. At three days there was considerable colloidophagy, and other phagocytes had foamy cytoplasm. There were some neutrophils in a few sites. Certain follicles were shrunken, empty, and devoid of colloid (Fig. 1). The autoradiographic pattern of the I^{131} was similar to that of the controls.

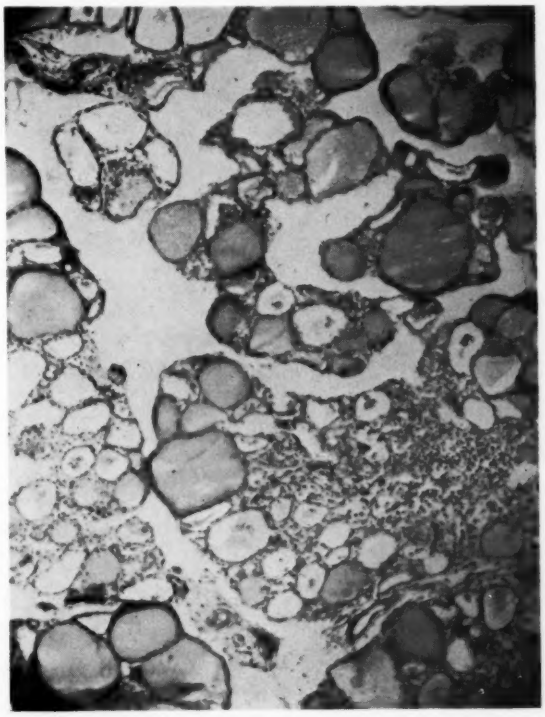


Fig. 1. Three days after 21,000 r. The thyroid gland has general preservation of architecture. Some phagocytosis of colloid is present, and some follicles appear shrunken and devoid of colloid. (Dog 320. Magnification ×100.)

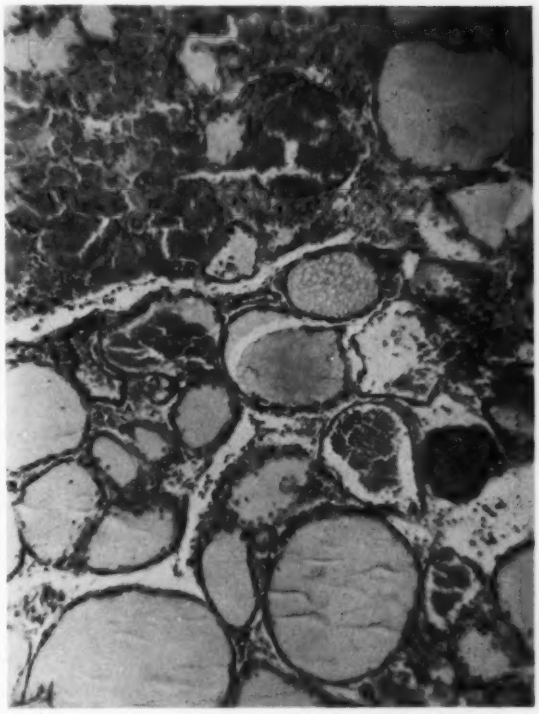


Fig. 2. Five days after 21,000 r. Hemorrhage into some follicles is noted and there are inflammatory cells in the interstitial tissue. There is no necrosis, and colloid is well preserved in this section. (Dog 321. Magnification ×100.)

In the animal studied at five days, one of the lobes was dark purple and hemorrhagic, and the other pale pink with focal hemorrhage. Microscopically, there was capsular edema and hemorrhage into some follicles. Scattered foam cells were seen. There were also phagocytes containing particles of colloid (Fig. 2). In this animal there was less damage and less removal of colloid than had been seen at three days. Most of the follicles had a normal appearing cuboidal epithelial lining and eosinophilic, fairly homogeneous, colloid. Autoradiograms showed the same patchy distribution of I^{131} as in the control animals.

Mottled, hemorrhagic thyroid glands were found in the 3 dogs studied at the seven-day interval. A more profound change in the histologic structure was now

evident (Fig. 3). Inflammatory cells and erythrocytes were infiltrating the capsule, which was somewhat edematous. Many follicles were shrunken and much of the colloid had been removed. The epithelial cells appeared viable, but in some instances they were displaced away from the basement membrane. The lumens of the follicles contained considerable numbers of phagocytes with foamy cytoplasm and occasionally globules of eosinophilic colloid remnants. In one of the dogs the altered follicles mingled with normal appearing follicles. In another animal a distinct "rim effect" was observed with a discontinuous border of normal follicles found in both lobes adjacent to the capsule and in a focal area near one pole. Autoradiograms in one instance showed at seven days a few of the more normal appearing follicles at the capsular margin to have more I^{131} than elsewhere. In another section a patchy follicular distribution of I^{131} was seen and a focus of radioactivity was detected in the wall of one vessel.

At the eight-day interval 2 animals were studied. In one of these (dog 314) some postmorten degeneration had occurred because the dog died some hours before autopsy. Hemorrhagic necrosis and focal inflammation were present. No satisfactory autoradiogram was obtained. In the other animal each lobe had one pole that was pink-tan while the remaining two-thirds showed diffuse hemorrhage and a sharp transverse line of demarcation. This was thought to represent the margin of the roentgen-ray beam, which in this dog did not completely cover the whole lobe; this was the only animal in which positioning of the beam was presumed faulty. In the irradiated area the changes were similar to those seen at seven days.

In the animal killed nine days after irradiation, the thyroid gland was larger than usual (2.36 gm.), firm and pink-tan, and had mottled areas suggesting hemorrhage. The abnormalities that had been observed at seven and eight days were also present in this gland microscopically. Most of the follicles were devoid of colloid or the colloid was apparently being phagocytosed. There was hemorrhage in the capsule, into follicles, and in the trabeculae. The epithelium was cuboidal and in the normal position, but at some points it was destroyed or displaced into the lumen. Autoradiograms showed that some of the preserved follicles had I^{131} activity in the colloid that remained. There was less radioactivity where colloid had been removed.

The animal dying at ten days showed postmortem degenerative changes. There was hemorrhagic necrosis, focal inflammation, and a ghost-like follicular pattern remaining.

The dog killed thirteen days after irradiation had hemorrhagic, purple thyroid tissue (weighing 4.67 gm.) that was firm in consistency. Microscopically, there was capsular edema, diffuse hemorrhage with scattered polymorphonuclear leukocytes and lymphocytes. Hemorrhagic destruction of most of the follicles had occurred. Some framework remained even with colloid-containing follicles persisting in one small group peripherally beneath the capsule. The autoradiogram showed the few follicles that were preserved at the rim to have retained some I^{131} activity (Fig. 4).

In the animal killed at fourteen days, the thyroid gland was hemorrhagic, firm in consistency, and weighed 2.67 gm. Microscopically, there was a diffuse infarction with interstitial hemorrhage and with scattered pyknotic nuclei. Indistinct outlines of follicles were recognizable. Vessel walls in the capsule were necrotic and thrombosed. No focal preserved follicles in the rim beneath the capsule were found in this gland.

(*c*) Dogs Receiving 10,000 r. In the animal killed eight days after irradiation, the thyroid gland was pale tan, and somewhat edematous. There was no gross hemorrhage. It weighed 2.0 gm. Microscopically, edema and lymphocytes were found in the capsular tissues (Fig. 5*A*). Many of the follicles had uniformly staining colloid and normally placed cuboidal epithelium. How-

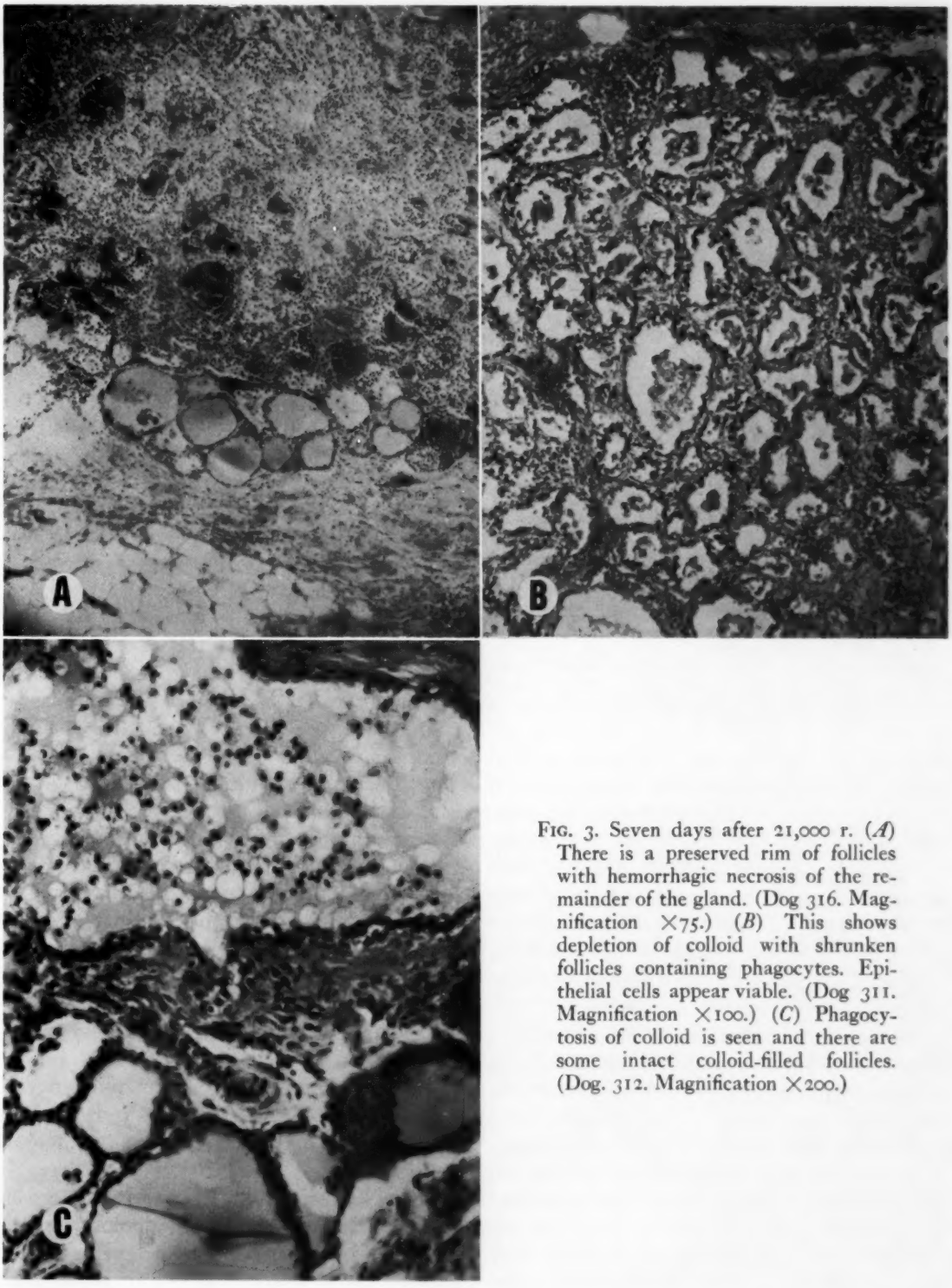


Fig. 3. Seven days after 21,000 r. (*A*) There is a preserved rim of follicles with hemorrhagic necrosis of the remainder of the gland. (Dog 316. Magnification ×75.) (*B*) This shows depletion of colloid with shrunken follicles containing phagocytes. Epithelial cells appear viable. (Dog 311. Magnification ×100.) (*C*) Phagocytosis of colloid is seen and there are some intact colloid-filled follicles. (Dog. 312. Magnification ×200.)

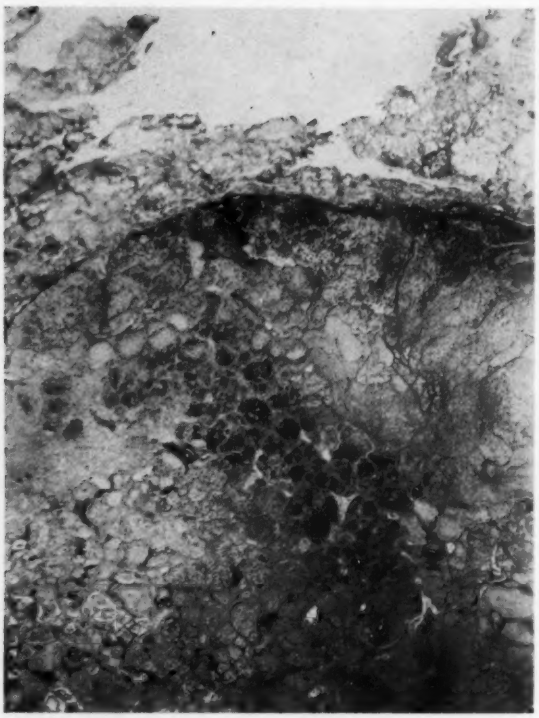


FIG. 4. Thirteen days after 21,000 r. In this area necrosis is complete and there is extensive hemorrhage; follicular framework can still be recognized. (Dog 307. Magnification ×20.)

ever, in many groups of follicles the colloid contained monocytic cells and desquamated cells with pyknotic nuclei. In some sites the colloid was gone. The interstitial tissue contained lymphocytes and phagocytes. The autoradiogram demonstrated a focal patchy activity chiefly concentrated in the larger follicles. At one site on the rim of one lobe, follicles had greater activity than those in the central portion of the gland.

In the animal examined thirty-one days after irradiation, one of the thyroid lobes was firm in consistency and the other was softer and had a zone of hemorrhage at one pole. In the first mentioned lobe there was a focal necrosis and some follicles contained phagocytes. However, most follicles looked normal and had uniform colloid. In the second lobe, although many follicles were normal, others showed shrunken acini with no colloid or with a thin granular colloid. Phagocytes and desquamated, pyknotic cells were in the lumens of these altered follicles. Several large vessels in the capsule contained nuclear debris and leukocytes; there was edema and fibrinoid degeneration of the muscularis (Fig. 5*B*). The autoradiogram showed patchy uptake of I^{131} with most of the activity in the moderate-sized follicles.

(*d*) Special Stains. Representative tissues were treated with Oil red O for fat. In control animals small droplets of fat-positive material were in the colloid of some follicles and occasionally in cytoplasm of follicular epithelium. There was no noticeable change in the numbers of these droplets in the animal at two and three days after irradiation. An interesting phenomenon was found in the animal killed at five days. Numerous phagocytes were observed within the colloid and these had foamy cytoplasm. Most of this foamy material did not give a positive fat reaction, but in some instances fat droplets were intermingled with the clear vacuoles. Somewhat increased numbers of fine granules of fat-positive material were also found free in the colloid and in some of the epithelial cells of the follicles. Similar changes were observed in the animals studied at nine days and thirteen days. The fourteen-day animal showed a similar picture but there was a relative increase in the amount of fat, which was distributed rather diffusely within the phagocytes and also in the colloid and epithelial cells. The animal studied thirty-one days after 10,000 r showed phagocytes in the follicles that were heavily laden with fat droplets but there was little or none in the epithelial cells. However, not all of the foamy material was fat.

Elastic van Gieson and phosphotungstic acid hematoxylin preparations were studied but no additional information was obtained from them.

The Gomori trichrome sections were of interest. The colloid, both in control animals and in those that had been irradiated, showed variation in the staining reaction. Most of it stained red, but here and there a few follicles had green staining colloid. At the time intervals characterized by removal of colloid from the follicles, some

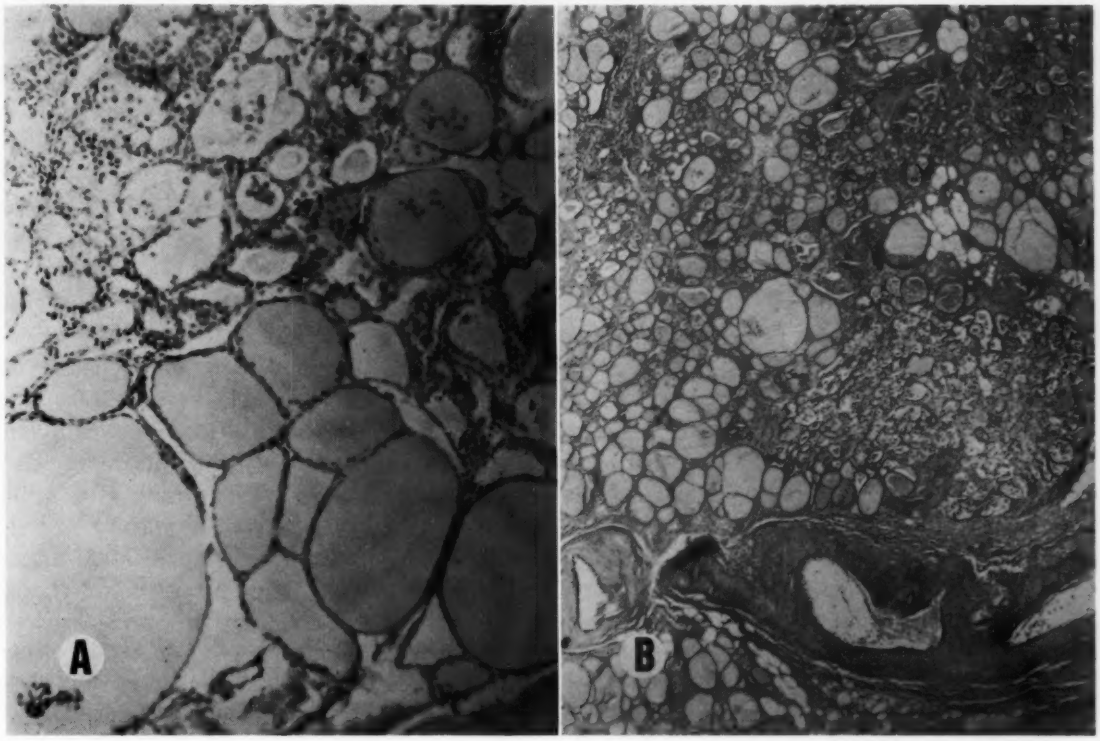


Fig. 5. After 10,000 r. The damage is not profound. (*A*) After eight days some colloidophagy is the chief abnormality. (Dog 319. Magnification ×100.) (*B*) After thirty-one days there are zones of focal necrosis with phagocytes filling follicles and fibrinoid degeneration and edema of vessel walls. (Dog 318. Magnification ×25.)

phagocytes were observed to have distinct globules, apparently of engulfed colloid. These globules seemed to stain red more uniformly than did the colloid of the follicles. Other phagocytes had only pale foamy cytoplasm.

In summary, the histologic sequence consists of a latent period followed by progressive degenerative changes. Following the latent phase, a second phase of rapid structural change begins with colloidophagy and the appearance of many shrunken, empty follicles but without complete epithelial necrosis. During this phase a "rim-effect" becomes apparent with intact islands of centrally placed larger follicles bordering the capsule and more advanced degenerative changes. Following this the picture is one of diffuse hemorrhagic necrosis.

DISCUSSION

The present study was undertaken as a sequel to the earlier one from this laboratory on the effects of large doses of I^{131}.[5] In both studies interpretation is limited by the individual variation of response and the small number of animals for each time interval. Study of the original data on thyroid I^{131} content and plasma I^{131} levels shows that there was great variation between different animals, rather than erratic daily variations in individual animals, accounting for the high standard deviations. A calculated dose of 60,000 gram roentgens was delivered steadily and uniformly to the thyroid gland during a period of sixty-seven minutes with external roentgen rays while the iodine yielded a beta- and gamma-ray dose that increased during the first twenty-four hours and gradually decreased thereafter. Furthermore, since the dose from I^{131} was supralethal, it is impossible to tell when this effective dose was delivered; it may have been reached any time during the latent period. With

such differences in the rate at which the radiation is delivered, efforts to make quantitative dose comparisons are useless. On the crude basis of total biologic response of the thyroid gland, the dose from the I^{131} appeared greater than that from the external radiation.

It is obvious that one would not recommend a single dose technique in trying to damage the thyroid tissue with external radiation and that a more favorable ratio of preservation of other tissues might be possible by a protracted treatment technique. The reasons why the external treatment effects cannot be validly compared with I^{131} effects have already been emphasized. Yet it is worth noting that with I^{131} it is possible to produce extreme damage to the thyroid tissue without obvious general radiation effects, whereas production of similar changes by a single treatment with an external beam of radiation limited to the thyroid gland area was fatal to the animal. The mechanism of illness and death after external irradiation is not clear; the limited data bearing on this suggest that local damage outside the thyroid gland was of great importance, with total body radiation effects not prominent.

Deposition of I^{131} in the thyroid tissue is uneven and consequently the radiation dose is uneven. There is some physical basis for believing that the edge of the gland receives a lower dose since the beta crossfire is not so uniform as it is in the more central portions of the gland. The dosage from externally applied radiation, although uniform at any given distance, rapidly decreases as the distance from the source increases. In the present study it is estimated that the difference between the dose on the anterior surface of the thyroid gland and that on the posterior surface was about ten per cent. The field was purposely extended well beyond the limits of the gland, and thus the edge of the beam presumably could not account for a rim of preserved tissue. In spite of these facts, there were, after external irradiation, islands of persistent follicles in the subcapsular region while the central portion showed severe degenerative changes. The fact that this "rim effect" can be produced by external irradiation throws great doubt on the explanation previously proposed for this phenomenon when seen after massive doses of I^{131}. The difference in "β crossfire" at the edge of the gland obviously cannot occur when a large external beam is used. Another explanation must be sought. Possibly the "rim effect" is related to the character of the vascular distribution.

In addition to the "rim effect," one of the points of interest was whether the effects of external radiation would be, in general, more uniform throughout the gland because of the presumably more uniform dosage distribution. We have noted, in some human thyroid glands, focal areas of necrosis preceding extensive hemorrhage or disturbance of the architecture as a result of I^{131} therapy. In the I^{131} dog series discussed here, the degenerative changes were quite sudden and massive and involved the whole gland, although not to a uniform degree. In the dogs given external radiation, there was also nonuniformity of the histologic damage in the gland at any stage. Thus in the two series no striking difference in the degree of uniformity of damage was demonstrated. Perhaps with lower doses of both types of radiation there would be a better opportunity to study this point.

The fact that a delay in onset of histologic changes was seen after external irradiation as well as with I^{131} weighs against the concept that in the I^{131} group the delay was solely due to the time required for build-up of radiation dosage.

We know of no previous reports of tracer studies showing a secondary rise in plasma I^{131} after external irradiation of the thyroid gland, although this phenomenon has been repeatedly noted following damage to the gland caused by internal radiation from massive doses of I^{131}.[5] In the present comparison of I^{131} with external radiation, this rise in blood radioactivity occurred somewhat later in the animals given external radiation. This perhaps correlates with the slower development of

necrosis and the presumed lower tissue dose in the externally irradiated animals. On the other hand, if the I^{131} released into the blood results from the removal of colloid, it is perhaps inconsistent with the histologic evidence of more prominent removal of colloid early after external irradiation.

A somewhat larger proportion of the I^{131} released into the blood is in the unbound form after external irradiation than after massive doses of I^{131}, but in both series the majority of the isotope released is protein bound. In the absence of further data on the exact form of the I^{131} released, it is believed that no particular emphasis should be put on this finding.

CONCLUSIONS

1. A single high dose of 21,000 r (60,000 gr.) of roentgen rays causes demonstrable accelerated release of iodine from the thyroid gland accompanied by severe degenerative morphologic changes.

2. The rise of I^{131} levels in the blood begins on the fourth day with a sharp peak on the seventh day and a subsequent gradual fall.

3. External measurements of I^{131} in the thyroid gland show an accelerated release of I^{131} from the gland, beginning on the fourth day and continuing until the tenth day, by which time most of the I^{131} has been lost from the gland.

4. Histologic studies show early changes at three days with increasingly severe degeneration at five, seven, and nine days followed by hemorrhagic necrosis at later intervals.

5. The latent period, showing neither functional nor structural changes, is an argument against the concept that the similar latent period seen after a high dose of I^{131} is due to the time required for the radiation dosage to build up.

6. Some follicles at the periphery of the thyroid gland remain intact in the presence of severe degenerative changes in the interior at certain intervals after external irradiation. This suggests a biologic rather than physical explanation for this same phenomenon when it is seen following massive doses of I^{131}.

Gould A. Andrews, M.D.
Oak Ridge Institute of Nuclear Studies
P. O. Box 117
Oak Ridge, Tennessee

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PRETHERAPEUTIC STUDIES WITH THE CHICAGO SYNCHROCYCLOTRON*

By S. D. WARSHAW† *and* D. G. OLDFIELD
CHICAGO, ILLINOIS

I. INTRODUCTION

SOME studies made of the properties of the high energy proton radiation generated by the University of Chicago synchrocyclotron are reported in this paper. This machine accelerates protons to an energy of 460 mev. with a nominal duty cycle of about 1 per cent. Until now it has had a serious defect, from the point of view of radiology, *i.e.*, the lack of high intensity external beam. The beam that was available for these studies, which are of a largely preliminary nature, consisted of that small fraction of the internal cyclotron beam that evades the well-known resonance blow-up at $n=0.2$ and escapes by symmetric emission around the perimeter of the "impact parameter" circle. The properties of this beam and the operation of the cyclotron have been discussed elsewhere.[6] Since this investigation was completed, some improvements have been installed[11] including a novel experimental shield, a strong-focusing condensing lens system, and a large steering magnet. The present beam intensity now is of the order of 100 rep/minute or more depending on the beam optics selected. The purpose of this paper is to describe the instrumentation and techniques used for the less intense beam; more detailed measurements using the more intense beam will be made in the future.

The instrumentation used for dosimetry and the results of measurements are given in Section II. The results of measurements on the relative biologic effectiveness (RBE) of protons near the end of their range, using organ weight changes in mice as an indicator, are described in Section III.

II. INSTRUMENTATION AND DOSIMETRY

A. *Instrumentation.* The primary physical problem in the use of any kind of radiation is the determination of the dose and the spatial distribution of the dose. High energy protons can be formed into a rather well-defined beam and have a well-defined range in materials. The general properties and advantages of such radiation, from the viewpoint of the radiologist, have been discussed in detail by Tobias, *et al.*[8] Some of the instrumentation in use at Chicago and some of the preliminary results on measurements of dose distribution for the low intensity beam are the subject of this section. The instrumentation bears no claim to originality, except in detail, but is a relatively simple and convenient setup for cyclotron radiology.

The basic dose meter was a modified thimble chamber (Fig. 1). Except for the metal parts, the entire cylindrical body of the chamber is cast out of Araldite 502,* an epoxy resin of low electrical conductivity. The ionization cavity is spherical, $\frac{1}{4}$ inch in diameter, with the inside surface coated with Aquadag. The collecting electrode is an aluminum wire that runs the length of the main tube and is insulated from the cylindrical guard electrode by teflon bushings; the remainder of the space inside the guard tube is filled with Superlawax. For this critical leakage region it was felt that the advantage of possible disassembly outweighed that of the easier fabrication obtained by filling this space with Araldite also. The cavity is formed by two hemispheres, one machined into the upper main casting and one into the lower casting. Electrical contacts are made within an aluminum fixture at the top of the main tube and brought out through a standard "Type HN" teflon-insulated connector for the signal, and "Type BNC" connector for the polarizing voltage. The measured

* Ciba Chemical Co., Kimberton, Pennsylvania.

* From the Argonne Cancer Research Hospital, The University of Chicago, Chicago, Illinois.
† Present address: Department of Physics, Hebrew University of Jerusalem, Jerusalem, Israel.

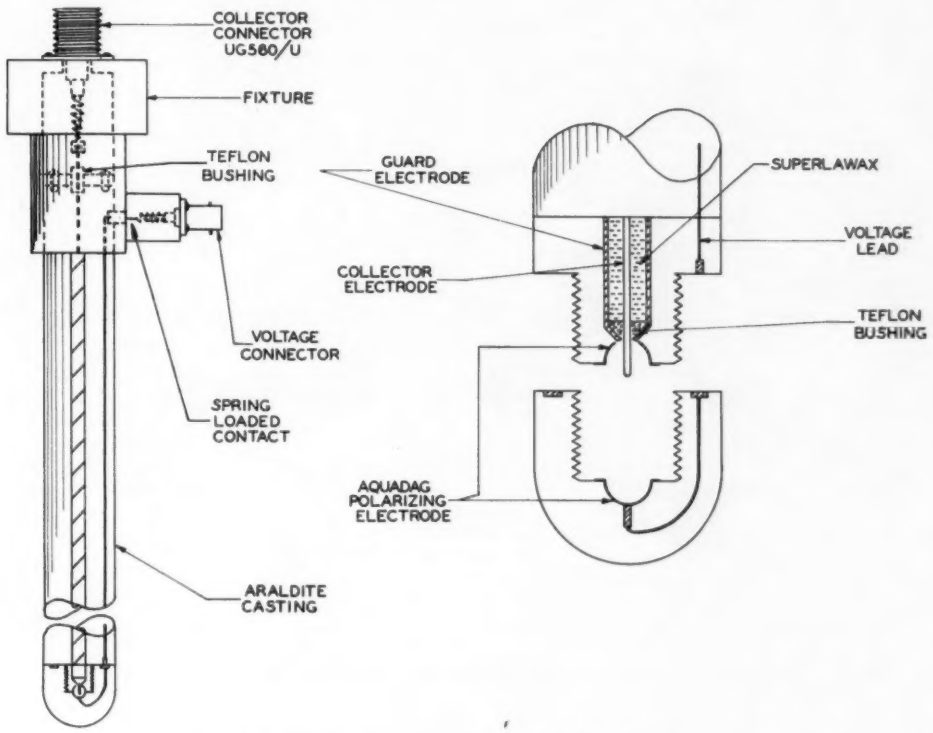

FIG. 1. Schematic drawing of thimble chamber.

leakage resistance from collector to guard was better than 10^{13} ohms. Since the density of the Araldite is nearly unity (about 1.1 gm./cm.^{3}) and it is an organic material mostly carbon and hydrogen, there is no first order correction for the wall material when this chamber is embedded in a tissue-like phantom.

Parallel plate chambers were used for general monitoring of the beam. These were constructed conventionally, of thin lucite plates made conducting with Aquadag, and a guard ring formed on the collector plate by scratching out the Aquadag with a sharp pair of dividers. They are $3\frac{1}{2}$ inches in diameter with $1\frac{1}{2}$ inches air space at atmospheric pressure.

External circuitry consisted of either a vibrating reed electrometer or a 100 per cent inverse feedback d-c amplifier with a CK5886 electrometer tube as pre-amplifier. The amplifier, designed originally for use as the "betatron health monitor"* is quite stable, showing less than 0.5 mv./hour zero drift rate after a two hour warm-up. A necessary modification was made in the mechanical construction of the pre-amplifier. It was found that the CK5886 circuit that was used responded to stray radiation, so that even in the absence of a chamber, any small fraction of the beam scattering into the pre-amplifier would give a signal. Therefore the pre-amplifier was enclosed in a steel can to shield against the stray magnetic fields present in the experimental area and filled with Superlawax. Input impedances were changed by means of plug-in units, each consisting of a modified HN-connector joined to a brass shielding tube containing the (potted) impedance. A switch was provided to short the grid to the feed-back point. (Before this unit was built, a remote control system using subminiature, low-leakage thermal relays was used to switch impedances in and out; this turned out to be more trouble than the advantage of remote control was worth.) A sketch of the pre-amplifier, showing the connections to the chamber and the plug-in impedance, is given in Figure 2. When

* By Mr. D. Connors.

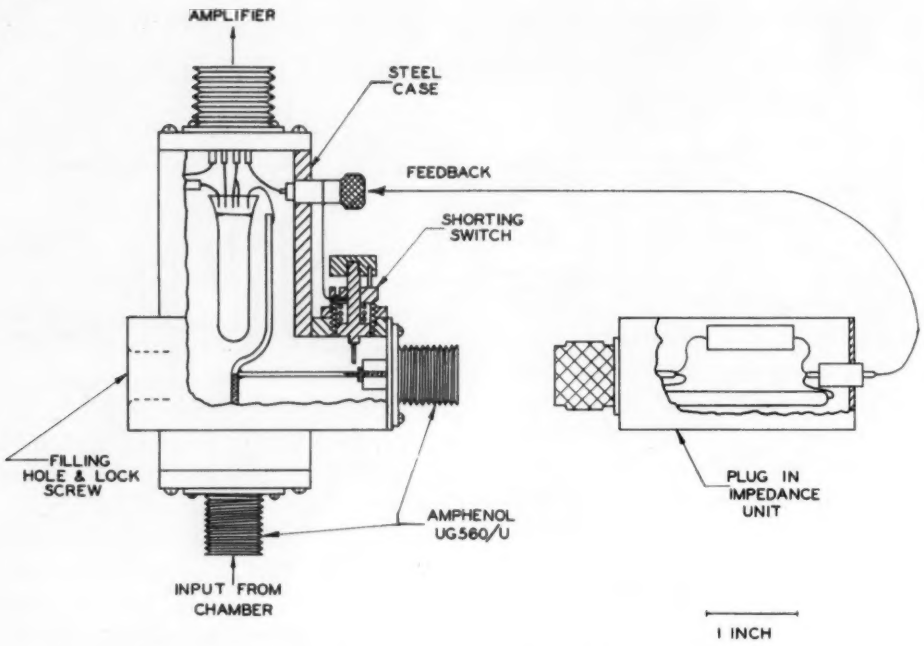

FIG. 2. Schematic drawing of pre-amplifier and plug-in impedance unit.

connection of the pre-amplifier to the chamber was not direct, it was made with a double-shielded, graphite-coated coaxial cable (Amphenol No. 21-406) that reduced pick-up and microphonic effects in the cable to a tolerable level. The high-level signal from the amplifier in the experimental area was then brought up through a long cable to the control area, where the signal was metered or recorded; the remote control box also had a "zero" adjustment for the d-c amplifier.

Auxiliary equipment included a Leeds and Northrup Speedomax recorder arranged to be used as a ratio meter; here, the battery used normally for balance was replaced by the signal from the d-c amplifier that represented the denominator of the ratio desired, and minor changes in the slide-wire circuit were made in the recorder. This was useful to locate beam axes by scanning with the thimble while using a flat chamber to monitor, or to quickly record Bragg curves. For accurate work—the transient response of the recorder not being adequate to accommodate the sometimes very rapidly fluctuating cyclotron beam—it was found preferable to measure the total charge collected, rather than the instantaneous ionization current. Having only a single vibrating reed electrometer, an electromechanical voltage-integrator circuit* was built. This device operates as an analogue computer, as is seen from Figure 3. The presence of the auxiliary feedback potentiometer makes it possible to use this circuit as an analogue for radioactive decay also, and therefore as an "activity computer."

In Figure 3, let N be the number of counts registered on the "units" dial (10 counts per shaft revolution). Let r be the fraction used of the sensitivity-adjust helipot R; the switch functions s_1, s_2, and s_3 are given in the inset to Figure 3 for any position of the (ganged) switches. Let V_{in} be the input voltage, k the coefficient of proportionality between the tachometer output voltage and the velocity of the output shaft, $V_{tach} = kdN/dt$, and let E be the full voltage applied across the feedback helipot. This potentiometer can be connected to any one of the shafts "units," "tens," "hundreds" . . . for which $n = 1, 2, 3, \ldots$ Then it can be shown very simply

* We would like to thank Mr. C. H. Wood for the construction of this device.

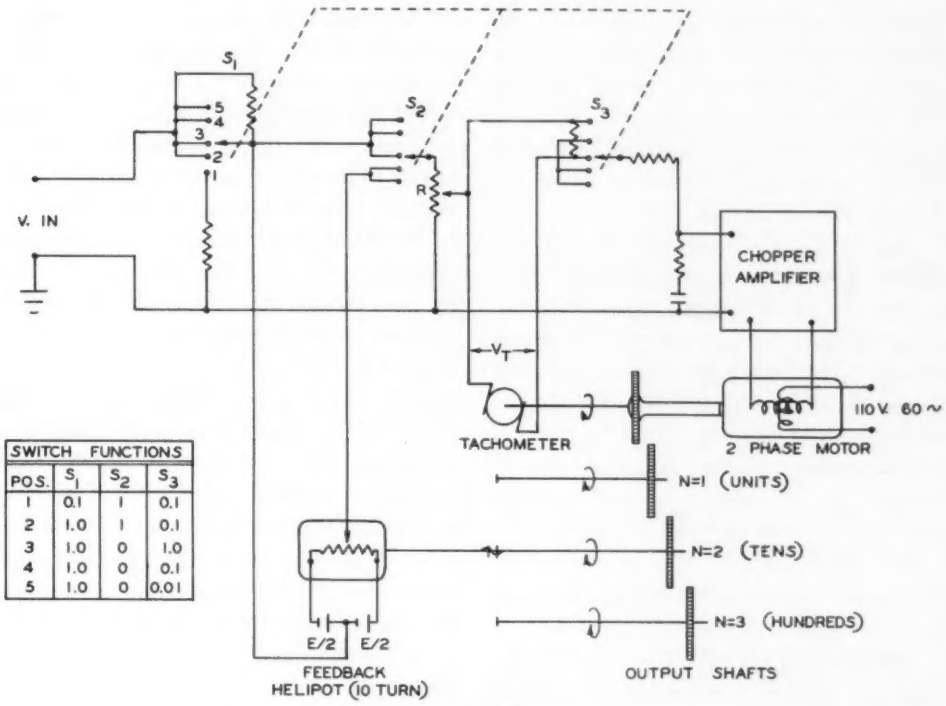

FIG. 3. Schematic drawing of integrator circuit.

that as the over-all system gain becomes large

$$\frac{dN}{dt}+\lambda N=\beta V_{\text{in}}$$

where

$$\lambda=s_2rE/s_3k10^{n+1} \quad \text{and} \quad \beta=s_1r/ks_3.$$

Thus, the device is, to a good approximation, the analogue of a target being activated, the activity decaying with a mean life $\tau=1/\lambda$ and the activating beam current proportional to V_{in}. While the beam is on, the register dials will turn at an ever decreasing rate; when the beam is turned off, the register will unwind at an exponential rate, the dial reading at any time being proportional to the activity of the target at that time. In switch position 3, 4, 5, $s_2=0$ $s_1=1$ so that

$$N=\frac{r}{ks_3}\int_0^t V_{\text{in}}dt.$$

The constant k has to be determined empirically by integrating a known constant voltage for a definite period of time. The device is limited in the range of input signals: for very small inputs it becomes nonlinear due to frictional drag in the tachometer, and for large signals the amplifier saturates. (Hence, the presence of the switch s_3, which in practice is set so that the ratio of output shaft speed to signal voltage is the same over a factor of 100 change in signal strength.) However, this limitation permits enough flexibility for most of our purposes.

For dosimetry, the thimble chamber plus integrator were used to establish the absolute dose, and the ratio of charge collected by the thimble (expressed as integrator counts) to the charge collected by the large flat chamber placed in the beam was determined; for actual exposures subsequently, the flat chamber was used to monitor the dose. Charge from the monitor chamber was measured on a low-loss capacitor* tied into the feedback loop of an Applied Physics Corporation vibrating reed electrometer. The output of this

* Obtainable from the John E. Fast Co., Chicago. These capacitors have better than 10^{14} ohms leakage resistance and a negligible amount of charge hysteresis effects.

instrument is recorded on a Brown extended-range recorder. The electrometer pre-amplifier, located near the chamber, was fitted with auxiliary relays so that the reed could be zeroed, or a resistor put in place of the capacitor, remotely from the control area. In addition, an extra polar switch wafer installed on the automatic range-switching shaft of the recorder permitted the use of a simple relay circuit. This was arranged in such a way that when the recorder pen carriage arrived at any pre-set dose, it tripped a microswitch, thus actuating the relay circuit which turned off the cyclotron pulser; at the same time, on-off signals could be furnished to other circuits, such as a clock or the voltage integrator.

The thimble chamber charge was converted to delivered dose by a simple calculation. Let $\dot{D}$ be the dose rate in rep per second; let n be the proton flux (protons/cm.^{2}/sec.), $(dE/dx)_w$ the stopping power of water in ergs/gm./cm.^{2}, w the energy needed to make one ion pair in air, and $q=93$ ergs/gm./rep. The ionization current is given by $i=\dot{D}V/3\times10^9$ where V is the chamber volume. This numerical relationship will be restated. In terms of the proton flux,

$$\dot{D}=\frac{n}{q}\left(\frac{dE}{dx}\right)_w.$$

Alternatively, the ionization current is

$$i=\frac{n}{w}\left(\frac{dE}{dx}\right)_{\text{air}}\rho V$$

where ρ is the density of the air (at NTP) in the chamber. Therefore $\dot{D}/i=Sw/Vq\rho$ where S is the stopping power of water relative to air. Using $w=32.2$ ev. and the measured volume of the thimble, assuming that it is all effective, this relation gives $\dot{D}/i=3\times10^9/V$ also, if $S\doteq1.04$ which is close to measurements at these proton energies.[1,8] The actual dose is then read off the integrator dials as described above. Errors in measurement (from the integrator and from the Victoreen resistor used in the input of the d-c amplifier) are estimated to be less than 2 per cent. The chamber calibration was checked by measuring the flux of protons that passed through it for a measured count. This was done by placing a foil (53 mg./cm.^{2}) of polyethylene (CH_2) in front of it and activating to get the reaction C^{12}(p, pn)C^{11}; C^{11} is a 20.5 minute positron emitter, and at the energy used for calibration, the reaction cross-section is 31 millibarns.[5] Since the activation times had to be about 30 minutes with the beam intensity available, it was necessary to make a correction for radioactive decay during the run and to account for fluctuations in the beam intensity. This was done automatically by the integrator now connected as an activity computer, by setting in the known mean life for C^{11}. However, it was realized that the many secondary neutrons produced in the chamber walls would in turn produce secondary protons of a lower energy than the primary beam. Since the reaction cross section at lower energies is three times the high energy cross-section, these would contribute to the foil activity (if the foil were mounted just in front of the thimble chamber) much more than their population warrants. Therefore in the measurement, the ratio of counts from the thimble chamber to the charge collected from the flat monitor, considerably upstream of the thimble, was first obtained. Before the activation, the thimble was removed and replaced with the foil, while the flat monitor remained; a secondary monitor, which was always in position, provided the signal to the activity computer. The resulting proton flux, when substituted in the above expression for ionization current as a function of flux, gave a thimble calibration within 2.5 per cent of the expected value, well within the errors of measurement of the carbon activity.

B. *Dosimetry*. It was desired to determine an RBE for proton exposure. Therefore the dosimetry measurements were done with this particular biological aim in mind. The high energy beam at Chicago is, at 460 mev., nearly minimum ionization radiation; it should therefore have an RBE, with respect to medium hard roentgen rays, of

nearly unity. Hence the measurement was to be made for protons of a lower energy, in fact about 4 times minimum ionization was chosen. It should be noted here that Tobias, *et al.*[8] have already reported that the RBE (using 30-day acute lethal dose in total body exposure of mice) for 340 mev. protons and for 180 mev. deuterons is approximately unity. Since the stopping power for 180 mev. deuterons is approximately the same as it is for 90 mev. protons, we should expect that the RBE for such protons, or protons of higher energy, would also be unity, at least if measured by acute lethal dose. However, since the use of organ weight changes, for certain organs, is a more sensitive criterion of radiation effects than acute radiation death, we could in fact hope that a measurable effect would be present at even 100 mev.

With the beam intensity low, at the time of these measurements, cutting down the energy to the required value by placing an absorber near the cyclotron (about 25 feet from the experimental space) was out of the question. Scattering in the absorber would have reduced the available intensity to too small a value for use. Therefore, the entire high energy beam was allowed to enter a long tank of water through a lucite window. (Note that the calculated range in water of 460 mev. protons[4] is 102 cm.) Since the beam is emitted from a localized "source" which has a rather complicated distribution in space, it was expected—and found—that the beam intensity profile was less uniform than might be desired. The beam, after "spilling out" from the cyclotron, first passed through the 0.01 inch thick aluminum port window of the vacuum tank, then through about 5 feet of air, then through a 5/8 inch collimator followed by a 9 foot long cylinder containing helium at atmospheric pressure and sealed by 0.008 inch Mylar windows. The function of the helium was to minimize the gas scattering between the exit and entrance collimators. Even for these high energy protons the multiple scattering angle in air over such distances becomes

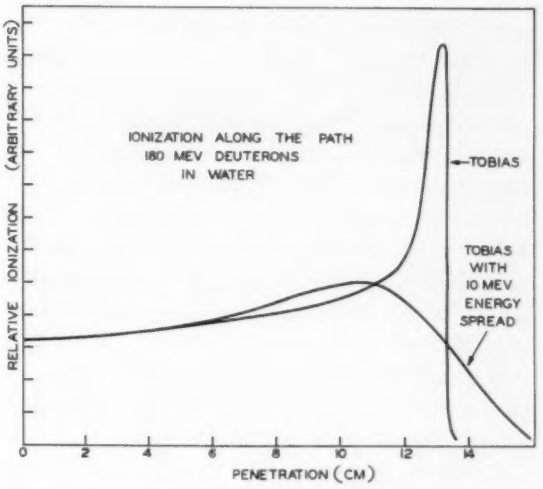

Fig. 4. Calculated effect of 10 mev. initial spread on Tobias' Bragg curve.

large enough so that a considerable fraction (about 10 per cent for this geometry) of the beam could strike the sides of the exit collimator thereby producing very many neutrons[2] and energy-degraded protons which would contaminate the experimental results. The exit collimator was about 2 inches in diameter, with the relative sizes of entrance and exit slits calculated from the known[6] beam divergence. Following the exit collimator, the beam passed through another 7 feet of air before entering the tank.

Under these conditions, as mentioned above, the dose distribution cannot be expected to be very flat in transverse section or sharply defined in range. In particular, the energy spread in the beam due to even the small amount of radial and phase oscillations, increased by straggling in the air path and windows, depressed the peak of the Bragg curve relative to the initial part and smeared the width of the peak considerably. Figure 4 shows the calculated effect* of an arbitrarily chosen 10 mev. spread given to Tobias' 180 mev. deuteron beam. His beam, by reason of an excellent focusing and deflection system is

* This was calculated by folding in a Gaussian spread to Tobias' sample curve. Let $i(x-R_0)$ be the ionization curve for zero energy spread and $g(R-R_0)$ be the distribution function in range of the initial beam with a mean range R_0. Then the ionization curve with a finite energy spread is $I=\int_0^\infty i(x-R)g(R-R_0)dR$. Here x is the residual range.

quite clean and the peak width appears to be due mainly to natural straggling. The small additional energy spread clearly produces a very pronounced effect on the range curve. At any rate, the net effect of a rather divergent beam, not very uniform in cross-section, with (by estimate) at least 1 per cent energy spread as it leaves the cyclotron would be to yield an isodose distribution which lacks a clear boundary at the edge and which does not have the well-defined, uniform "hot-spot" that is characteristic of heavy, charged radiation near the end of its range. Therefore, it was considered inadvisable to make total body exposures with the animals at the Bragg peak since the dose distribution over the animal would be nonuniform. Since it was also desired that the animals be exposed at as low an energy as possible, this meant that they would have to be placed in the beam just before the rise in ionization toward the end of the range.

Measurements of the isodose distribution were made with the $\frac{1}{4}$ inch cavity chamber. The chamber was mounted to the moving stage of a scanning unit; this consisted of a 20 inch long lead screw which moved a carriage in the x-direction and on the carriage another lead screw which moved the stage (and chamber) in the y-direction. Both motions were effected remotely through small motors. No z-motion was available on this unit, and therefore the center of the chamber was positioned precisely (using a telescope directed along the known beam direction) so as to be in the center of the beam along the entire length of travel. The signal from the cavity was integrated and integrator counts recorded for a fixed amount of charge recorded on the electrometer, connected to the (non-moving) monitor. A series of beam profiles, dose *versus* y at different values of x then yielded by graphic construction the isodose distribution given in Figure 5. Note that the desired hot-spot is clearly visible but it is not nearly so striking as that given in Reference 8. Only the last one-third of the range of the 460 mev. protons is shown. This figure is reproduced without comment, since it is only an approximation to the desired distribution. The ultimate requirement is, of course, a very intense Bragg peak which can be exploited in the treatment of deep tumors. A Bragg peak-to-valley ratio of, say, 10 to 1, and RBE for tumor damage of only 2 means that a small tumor could be irradiated with 20 times the effective dose given to the skin. Work is now in progress with the new installation at Chicago to improve this distribution.

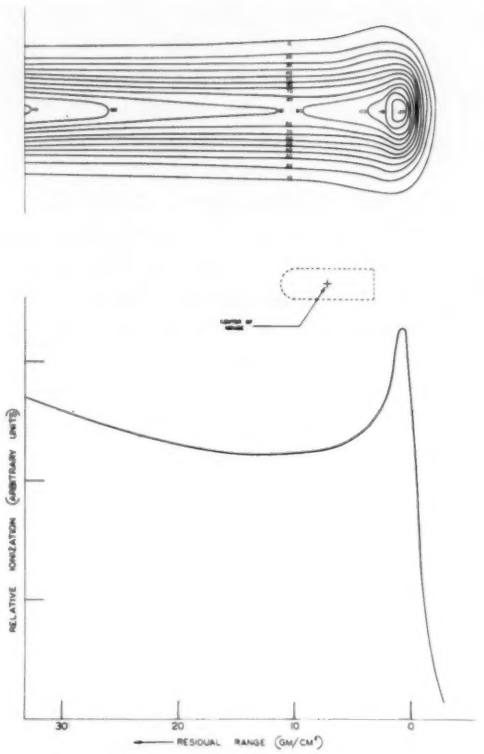

FIG. 5. Isodose distribution and Bragg curve for the last one third of the range of 460 mev. protons in water.

Finally, the mice for the experiment to be described in the next section were enclosed in lucite tubes (with air intake and exhaust) and placed in the water such that the residual range of the primary beam at the center of the tube was 7 gm./cm.^{2} This corresponds to a proton energy of about 90 mev. and at this energy $(dE/dx)_w = 8$ mev./gm./cm.^{2}, while minimum ionization in water is 2.07 mev./gm./cm.^{2}.

III. RELATIVE BIOLOGICAL EFFECTIVENESS (RBE) MEASUREMENTS

A discussion of an interpretation of organ weight changes after radiation exposure has been given in another paper.[10] Here some measurements of spleen and thymus weight loss will be given and analyzed with a view toward getting a measure of an RBE for the proton beam. It is to be emphasized that the final number for RBE has an uncertain biological significance if taken at quantitative face value. However, it is also true that within an uncertainty that is exclusive of random errors of measurement the RBE indicates a difference between the effects of different kinds of radiation, and this difference may very likely apply to a wide class of biologic material. (The reasons for the uncertainty are considered in Reference 10.)

The physical dosimetry has been discussed at length in Section II. This section will deal with the RBE for protons slowed from 460 mev. to a mean of 90 mev., with total body exposure, the reference radiation being 250 kv. roentgen rays (target distance = 82 cm., current = 30 ma., nominal dose rate = 16 r per minute, filtration = 0.5 mm. Cu + 1 mm. Al) from a General Electric "Maxitron. Exposure to the Maxitron was made with the animals in plastic tubes on a thick lucite tray, and with the dose measured by a Victoreen thimble chamber inserted in one of the animal tubes during the exposure; roentgens were converted to rep by multiplying by 93/83 as usual.

A. *Biological.* The mice used were strain LAF_1* males with an average age of 7 weeks. For the animals bred in the Argonne Cancer Hospital animal farm it was not possible to ensure that effective randomization across litters was made. Since relatively few mice are weaned each week, no record was kept of the litter-origin of each mouse. In a grand average of many separate runs, over many months, however, any discrepancies from this cause should have averaged out. In any experimental run, selection of mice was made by total body weight; the animals were housed 10 to a cage, with each cage to receive a specified dose. The mean body weights, across cages, were adjusted to be equal—within one standard deviation—and animals whose body weights differed from the population grand average before selection by more than one standard deviation were rejected. One large group of these animals was obtained from a commercial supply firm, and used to establish the roentgen-ray regression. For these animals, while the thymus weights were not significantly different from the mean weight of thymus controls for the Argonne animals, the spleen weight was nearly twice as great and the total body weight considerably different. The coefficient of variability for thymus-spleen for the commercial animals was larger than for the home grown variety. (Pathologist's findings for possibly diseased animals were negative, although this abnormal spleen weight is itself probably symptomatic of disease.) Since the reason for using this strain was the hope that its highly inbred character would lead to a homogeneous population, this result was rather disappointing. Table 1 shows a comparison of spleen and thymus weights for the Argonne, the commercial, and 7–8 week old CF No. 1 males purchased from Carworth Farms. The population samples for the LAF_1 commercial were chosen from among the best, in terms of variability, of those available; the samples of LAF_1 Argonne were about average. Evidently there is no tremendous advantage in using the rather expensive LAF_1 strain.

After exposure, the animals were replaced in their cages and stored in the same room as the control animals. At 5 days post-exposure, controls and exposed animals were sacrificed in ether and the spleen and thymus excised. The spleen was weighed immediately after excision; the thymus was fixed in 10 per cent formalin solution for 24 hours, the adherent fatty tissue teased off, and then weighed.[3] An auxiliary experiment confirmed (Table II) that the ratio of wet to dry weight for thymus remained

* More specifically, $(C_{47}L/He \times A/He)F_1$.

TABLE I

COMPARISON OF HOMOGENEITY OF SEVERAL MOUSE POPULATIONS

Strain	Spleen		Thymus	
	Mean of 10 (mg.)	σ (Per Cent)[b]	Mean of 10 (mg.)	σ (Per Cent)
LAF_1 Argonne	98.1	19	43.7	24
	94.9	23	35.8	29
LAF_1 Commercial[a]	173.3	23	43.7	39
	181.0	42	38.0	35
CF_1	118.0	33	39.2	23
	101.9	30	35.1	33

[a] Variance analysis between the commercial and Argonne spleen groups shows that they are *not* of the same population to better than the 1 per cent confidence level. The same analysis for thymus shows that they *are* randomly selected to the 1 per cent level.

[b] Each pair of means were of the same randomly selected population to the 5 per cent level.

constant for both exposed and control animals.

The dry weight was obtained by vacuum desiccation of the fixed organs for 24 hours. The water loss after 24 hours became negligible; desiccation of unfixed organs gave essentially the same result but with a greater variance, since it was considerably more difficult to tease off the adherent fat from the fresh organ.

Tests for statistical consistency in the wet versus dry experiment and in all other data of this article that were in doubt were

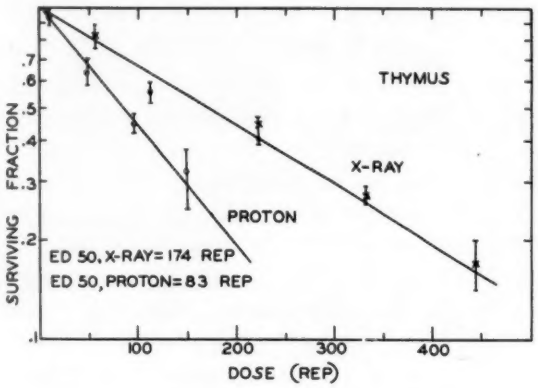

FIG. 6. Surviving fraction of thymus; ED 50 = effective dose for 50 per cent survival.

made by a Fisher variance analysis[7] and population homogeneity checked to better than the 5 per cent confidence level. Occasionally, single animals were rejected from a sample if the isolated weight differed from the mean by more than three standard deviations.

B. *Results.* The results are expressed as the ratio of exposed organ weight to control organ weight and designated S, for surviving fraction. The standard error of estimate for weights was used to convert to an estimated error in S. Figures 6 and 7 show the measured S for thymus and spleen versus the dose expressed in rep. In the case of spleen (roentgen ray, commercial animals), while the spleen weight was wildly different from that of the Argonne animals, the ratio of exposed organ weight to control weight (S) turned out to be *not* significantly different. The S-values taken with the commercial animals are marked as solid

TABLE II

WET AND DRY THYMUS WEIGHTS

Dose (r) (Roentgen-ray)	No. Mice	Mean Weight (mg.)				Ratio Dry/Wet
		Wet	Coefficient of Variability (%)	Dry	Coefficient of Variability (%)	
0	20	45.2	17	10.0	22	$.221 \pm .058$
100	20	25.3	19	5.1	24	$.202 \pm .062$
200	25	18.0	20	4.0	16	$.222 \pm .056$

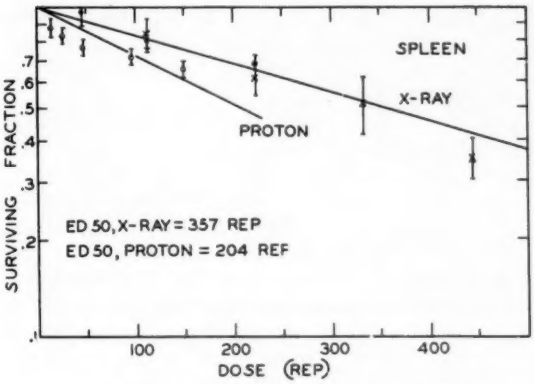

FIG. 7. Surviving fraction of spleen; ED 50 = effective dose for 50 per cent survival.

points of Figure 7. The data were fitted by least squares with curves of the form $S = exp(-D/D_0)$ in accordance with the appendix to Reference 10. Table III gives the values of D_0 for each of the 4 cases.

TABLE III

DOSE SENSITIVITIES FOR SPLEEN AND THYMUS WEIGHT CHANGES WITH EXPONENTIAL REGRESSION

	D_0 (Roentgen-ray) (rep)	D_0 (Protons) (rep)	R = RBE
Spleen	515 ± 32	295 ± 33	1.75 ± .23
Thymus	250 ± 5.8	120 ± 4.1	2.08 ± .07

IV. DISCUSSION OF RELATIVE BIOLOGICAL EFFECTIVENESS (RBE) MEASUREMENT

From Table III it can be seen that although the experimental error in the spleen determination was larger than that for thymus, the two results are substantially the same, that is, the RBE with respect to 250 kv. roentgen rays is about 2. It was stated above that the RBE obtained by Tobias, *et al.*[8] was approximately unity, for roughly corresponding radiation, as measured by acute lethal dose in total body exposure. It seems not unreasonable that the two results do not agree since death is a drastic and arbitrary response which involves a complex of prior responses including, for example, the loss of function of certain vital organs. However, the results are not in satisfactory agreement with those of Carter, *et al.*, and Bond, and Seymour.[3] These authors report that the RBE for neutrons ranging in energy from 3 mev. to 20 mev. was 1.6 using mortality, 1.7 using spleen weight loss, and 1.5 using gut weight loss as indicators. It is true, of course, that some differences in the two experimental results can be accounted for by strain and sex differences, and in particular, by normal organ growth differences (see Reference 10). However, their result that mortality as indicator yields the same answer that the organs do is rather surprising. The neutrons used in their experiment produced a recoil spectrum of protons that varied from about 10 times minimum ionization to several times this figure, and we should have expected that the RBE measured for these neutrons would be considerably larger, by any endpoint, than the roughly 4 times minimum ionization (in the middle of the mouse) protons used in the present experiment. Carter, *et al.* state that there is probably no marked variation in RBE over the neutron energy range from 3 to 20 mev. since their results agree with those of other workers using 14 mev. monoergic neutrons. However, the recoil proton spectrum from a 3 to 20 mev. spectrum of neutrons will look rather similar to that from a 14 mev. monoergic beam, although more peaked at higher specific ionization. Therefore, those two results should have been rather close.

Assuming that Carter's statement is correct, then the results of the present experiment imply that its validity might extend down to a mean specific ionization about 4 times minimum. Since the dosimetry for the neutrons is somewhat uncertain, such a conclusion is speculative.

The work of Vogel *et al.*[9] is more consistent with our own results. Using fission neutrons, these authors found an RBE of 4.5 or more with respect to Co^{60} gamma rays. Since the RBE for gamma radiation is 0.5 with respect to 250 kv. roentgen rays, Vogel's result is RBE = 2.3 on the same

basis, and therefore larger than the slightly less than 2 we have found.

SUMMARY

Instrumentation and dosimetry for the high energy proton beam of the University of Chicago synchrocyclotron is described. Since the beam is of usable but low intensity, and equipment for increasing its intensity and for focusing it to get a good isodose distribution has only recently become available, these studies are to be considered of a preliminary nature. The beam was slowed down to a residual range of 7 gm./cm.^{2} of water (from an initial 107 gm./cm.^{2}) in a long water tank. The relative biological effectiveness (RBE) at this point was measured with respect to 250 kv. roentgen rays using the technique of mouse spleen and thymus weight change observed 5 days after exposure. The result was RBE = 1.75 ± .23 (spleen); RBE = 2.08 ± .07 (thymus).

D. G. Oldfield
Accelerator Building
5604–20 Ellis Avenue
Chicago 37, Illinois

We would like to thank Dr. R. E. Carter for his interest and suggestions, and Miss L. Latsis for performing the tedious biological labor.

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HEMATOLOGIC RECOVERY OF ADULT AND WEANLING RATS FOLLOWING WHOLE BODY ROENTGEN IRRADIATION*

By ROBERTS RUGH *and* JOAN WOLFF
NEW YORK, NEW YORK

RATS respond rapidly to whole body roentgen irradiation by drastic changes in the peripheral blood. It is of interest to determine the rate and the degree of this response in the weanling as compared with adult rat, as well as the rate and the degree of their recovery. After full hematologic recovery from the initial roentgen irradiation, the rats were allowed to rest for two months following which they were re-irradiated and the hematologic sequelae were determined. The data throw light not only on the rate and degree of response and recovery, but the differences in response between the weanling and adult rats.

MATERIALS AND METHOD

White Wistar rats were used which had been raised in our laboratory. These rats had been bred from a strain which showed a very low incidence of respiratory ailments.

The three adult females used were between six and nine months of age. The 6 weanlings were six weeks of age at the time of roentgen irradiation. The latter included 4 females and 2 males.

The roentgen facilities included a Quadrocondex constant potential roentgen therapy machine run at 210 kv. peak and 15 ma. at a target distance of 50 cm. from the mid-body level of the rats, and at a rate of 96.6 r/min. air dose. The total dose used was 600 r administered in 6.1 minutes. This is somewhat less than the accepted $LD_{50/30}$ day dose level and all rats survived both the initial and the repeated exposures. Blood samples were taken from the tail of each of the 9 rats twice during the week prior to exposure and either two or three times weekly thereafter. Each analysis included: A. *Leukocytes:* (1) total white blood cell count; (2) differential white blood cell count* (lymphocytes, neutrophils); (3) platelet count. B. *Erythrocytes:* (1) total red blood cell count; (2) hemoglobin percentage. C. *Abnormal cell types:* (1) Nucleated erythrocytes; (2) lymphocytes with bilobed nuclei.

Following the initial whole body roentgen irradiation with 600 r, the above blood analyses were made on every rat for a period of forty-six days, or until plateaus of recovery had been reached. A period of two months' rest then followed during which the rats were given the usual care, food and water in our animal quarters. Then all rats were re-examined for blood determinations for a period of one week prior to re-irradiation to the same dose level as previously. Thereafter peripheral (tail) blood samples were taken for analysis two or three times weekly for a total of fifty days, again a time when plateaus had been reached. Before concluding the experiment, two additional sets of data were collected at eighty-four and eighty-nine days after the second exposure, or one hundred and seventy-five days (approximately six months) after the experiment had been initiated.

EXPERIMENTAL DATA

Adult Rats (3 females)

A. *Leukocyte Count* (Fig. 1).

(1) *Total white blood cell count, absolute value.*

The average count of white blood cells made on the adult rats during the week prior to roentgen irradiation was 10,730 and the

* The other cellular elements occurred in such small numbers that the data would be less significant.

* Based on work performed under Contract AT-30-1-GEN-70 for the Atomic Energy Commission.

range was 8,050 to 16,050 per cubic millimeter.

Twenty-four hours after whole body roentgen exposure to 600 r, the average count for the 3 rats dropped to 1,730 and by seventy-two hours it dropped to the lowest level of 517 cells per cubic millimeter. Thereafter, there was gradual recovery to 6,630 at forty-six days. This was not complete recovery, however. After two months of rest and prior to the second exposure the white blood cell count reached an average of 10,070 with a range of 6,800 to 12,750. Thus, there was evidence of almost complete recovery by fifteen weeks after 600 r roentgen irradiation.

Following re-irradiation at fifteen weeks, there was again a precipitous drop to 550 in the average total white blood cell count at five days and the lowest level was 467 at eight days. This was not appreciably different from the drop after the first exposure. However, recovery was different in that among the rats (1 was accidentally killed forty-seven days following the second exposure) the white blood cell count recovered more rapidly and attained a level of 7,350 by fifty days. At the termination of the experiment, eighty-nine days after the second roentgen irradiation, the average leukocyte count was 14,125 or somewhat higher than at any previous time. The range was 12,000 to 16,250. Whether this was a preleukemic condition was not determined, as the rats were sacrificed (Fig. 1).

(2) *Differential white blood cell count, relative values.*

a. *Lymphocytes:* The lymphocyte count of adult rats prior to roentgen irradiation averaged 73.5 per cent of all of the white blood cells. This dropped to 13 per cent by twenty-four hours postirradiation, and to 8.7 per cent at seventy-two hours. The percentage then climbed gradually to an average of 64 per cent at forty-six days, still less than the preexposure level of 73.5 per cent.

After the two months' rest period the lymphocyte percentage of all white blood cells again was normal, at 74.5 per cent. Following the re-irradiation to 600 r it dropped to 20 per cent by twenty-four hours and then rose steadily to 42 per cent by the eighth day. The recovery rate was slower than that following the initial exposure and at fifty days was only 51 per cent. While this was somewhat less than at the same interval of time following the first exposure, at eighty-nine days after the second exposure it dropped further to 40.5 per cent so that there was evidence of failure at complete recovery of lymphocyte production.

b. *Neutrophils:* In contrast with the lymphocytes, the neutrophil percentage of white blood cells was increased (even though the absolute count was reduced) by roentgen irradiation of the rat. Prior to exposure the neutrophil average for the adult rats was 23.4 per cent of all white blood cells and by twenty-four hours after exposure this ratio had increased to 86.3 per cent. By three days it was at the highest level of 91 per cent. The count then dropped gradually to 31 per cent at forty-six days, which was, percentage-wise, still higher than the pre-irradiation level of 23.4 per cent.

After two months' rest the neutrophils averaged 22.5 per cent of all white blood cells which was a value quite close to the level prior to roentgen irradiation. By twenty-four hours after re-exposure the average was 80 per cent but this dropped, after erratic shifting, to a low of 47.5 per cent at fifty days and 49.5 per cent at eighty-nine days. Thus, there appeared to be a permanent elevation in the neutrophil percentage with relation to the total white blood cells by the two irradiations from 23 per cent to 47.5 per cent.

Absolute Values, Number of Cells per Cubic Millimeter. It must be pointed out here that we have been presenting percentage values with respect to the total white blood cell count and not absolute values. The erroneous impression may be gained that there was an actual increase in neutrophils, for instance, while there was actually a drop in absolute numbers. This was represented as an increase in percentage values only with respect to the total white blood cell count, which itself

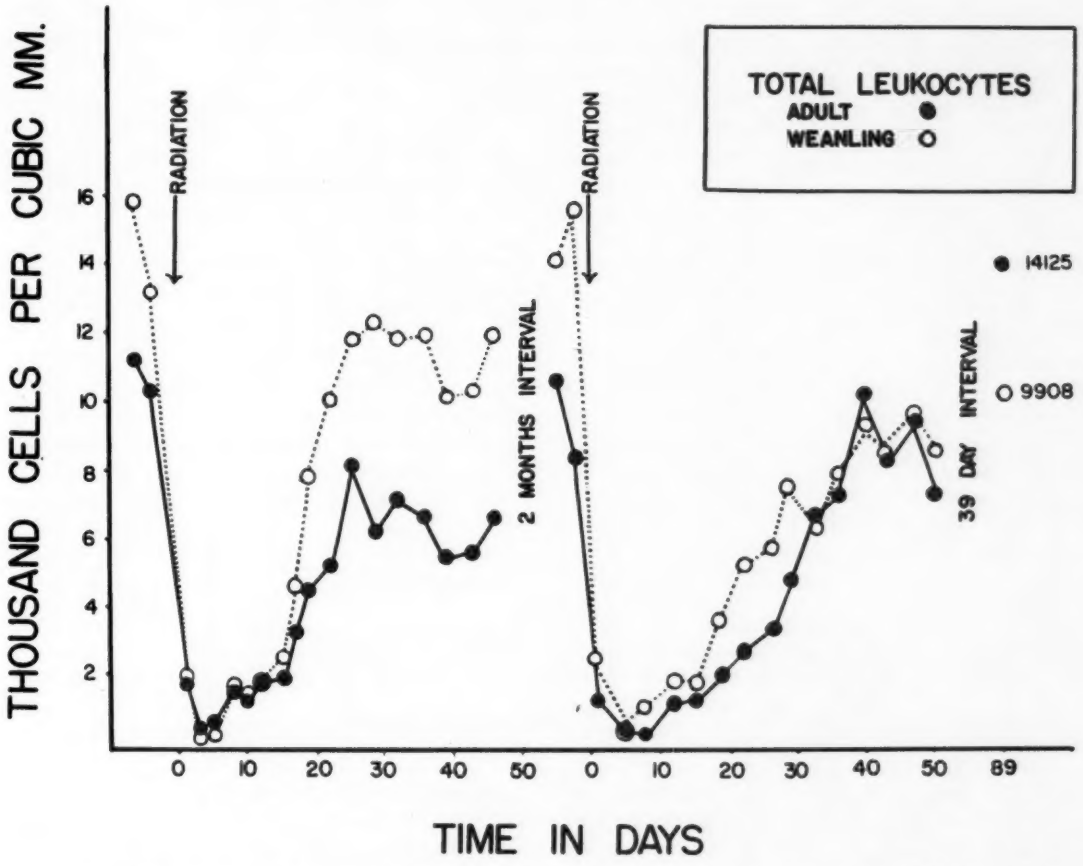

Fig. 1. Total Leukocyte Count in Weanling and Adult Rats. The total leukocyte count in the weanlings was somewhat higher than that in the adults, but following roentgen irradiation the depression in these counts was approximately at the same level. Recovery of weanling leukocyte count was more rapid than recovery in the adults. At the time of re-irradiation the weanling count was still higher than that of the adults, and this was caused to drop to the same level as after the first exposure by three days. This time the weanling recovery of leukocytes was similar to that of the adults, possibly because they were now chronologically adults also. The final leukocyte count for all rats was below that of the pre-irradiation level.

dropped following roentgen irradiation.

In Table 1 is illustrated the difference between the absolute and the relative values of lymphocytes and neutrophils. This table illustrates the following: Delayed recovery in leukocytes following the second exposure; leukocytosis at the termination of the experiment; permanent slight lymphopenia; and three times absolute increase in neutrophils at termination of experiment.

(3) *Platelet count, absolute value* (Fig. 4).

The average number of these cells was 494,000 per cubic millimeter in adult rats, with a range of 322,000 to 604,000. The platelet count did not respond as rapidly to roentgen irradiation as did other "white" cells, so that by twenty-four hours after exposure the average was 410,000 and by three days it was down to about half or 250,000. The lowest level was reached by ten days after exposure and was 27,000. By forty-six days it had climbed to 260,000 still far below the pre-exposure level of 494,000.

After two months' rest the platelet count of these adult rats had reached an average of 373,000. This was still below the pre-exposure level of 494,000. Full recovery was, therefore, not attained. Upon re-irradiation, the count showed an average

TABLE I

SUMMARY OF WHITE BLOOD CELL COUNTS*
ADULT RATS

Time	Total Leukocytes (Fig. 1)	Lymphocytes (Fig. 2)	Neutrophils (Fig. 3)
	Per Cent	Per Cent	Per Cent
Before Irradiation	11,230 (100)	8,310 (74)	2,695 (24)
1 Day After	1,730 (15.4)	225 (13)	1,488 (86)
3 Days After	517 (4.6)	45 (8.7)	470 (91)
8 Days After	1,517 (13.5)	319 (21)	1,183 (78)
46 Days After	6,630 (59)	4,243 (64)	2,055 (31)
	Two Months Respite		
Before Irradiation	10,075 (100)	7,456 (74)	2,317 (23)
1 Day After	1,250 (12.4)	250 (20)	2,317 (23)
8 Days After	467 (4.64)	196 (42)	257 (55)
50 Days After	7,350 (73)	3,749 (51)	3,528 (48)
84 Days After	12,725 (116)	5,726 (45)	6,235 (49)
89 Days After	14,124 (140)	5,791 (41)	7,063 (50)

* Absolute values. Percentage values in parentheses. Leukocyte percentages are related to the pre-irradiation leukocyte count as 100 per cent. Lymphocyte and neutrophil percentages relate to total count per cubic millimeter of the same animals at the same time.

of 385,000 at twenty-four hours. The lowest level was achieved at twelve days and was 32,000. By fifty days after exposure the count was 326,000 and by eighty-nine days it had reached the high level average of 480,000 which was very close to the control level. Thus, the platelet count appeared to make complete recovery in the adult rats.

B. *Erythrocytes, absolute value.*

(1) *Total red blood cell count.*

The average of 6 counts made on 3 rats prior to the initial roentgen irradiation was 9.3 million cells per cubic millimeter. Following roentgen irradiation to 600 r the count did not drop rapidly. It reached its lowest level of 5.47 million at seventeen days, and then increased until it reached 7.88 million at forty-six days. This was not complete recovery.

There was then a two months' rest period after which the count was 8.56 million. This was still below the original pre-exposure average of 9.3 million. The post-irradiation drop, however, was greater after the second roentgen irradiation and reached a low of 2.63 million at fifteen days. The count then climbed gradually to 6.58 million at fifty days and 7.10 million at eighty-nine days. Thus, there was a degree of permanent anemia in the adult rats caused by each exposure, and the cumulative effect resulted in a 23.4 per cent drop in the erythrocyte count.

(2) *Hemoglobin percentage.*

The pre-irradiation average of hemoglobin in the adult rats was 93 per cent and this showed a slight drop to 88 per cent by twenty-four hours after exposure to 600 r and to a low of 63.5 per cent at twelve days. In contrast with other blood analyses, recovery to 93 per cent was complete by forty-six days. However, after two months of rest the hemoglobin percentage was down slightly to 83.5 per cent. It dropped to a low of 34.4 per cent some fifteen days after re-irradiation. It then climbed gradually to 85.5 per cent at fifty days and held this at eighty-nine days. Thus, after two exposures, each consisting of 600 r whole body irradiation some fifteen weeks apart, the hemoglobin percentage showed only a very slight drop of 7.8 per cent.

Weanling Rats (4 females, 2 males)

The data for six weanling rats are averaged together in the following report. The individual

records for the males and for the females showed the usual fluctuations without any consistent sex differences.

A. *Leukocyte Count* (Fig. 1).

(1) *Total white blood cell count, absolute value.*

The pre-irradiation (control) white blood cell count of the six week old weanling rats was 13,540 cells per cubic millimeter. One day following whole body roentgen exposure to 600 r this dropped to 1,900 or 13 per cent of the original value. By the third day it was still lower, 233 cells or 1.6 per cent. Nevertheless, these weanling rats began to show recovery by the fifth post-irradiation day (408 cells) and by forty-six days the count was 11,970 which could be considered as quite normal.

The two months' rest period allowed complete recovery to 14,940 cells. However, one must point out that by this time the original weanling rats were about four months of age and were essentially mature. When we compare the leukocyte count of these rats, irradiated while weanlings but which had recovered and matured, we find that the white blood cell count is somewhat above that of the pre-irradiated adult rats (14,940/10,730).

When these "recovered" weanlings, now adults, were again irradiated with 600 r, there was again an immediate drop in the leukocyte count to 2,508 (17 per cent) by the first day and to 450 (3 per cent) by the fifth day. From such a leukocyte depression the "grown-up weanlings" then

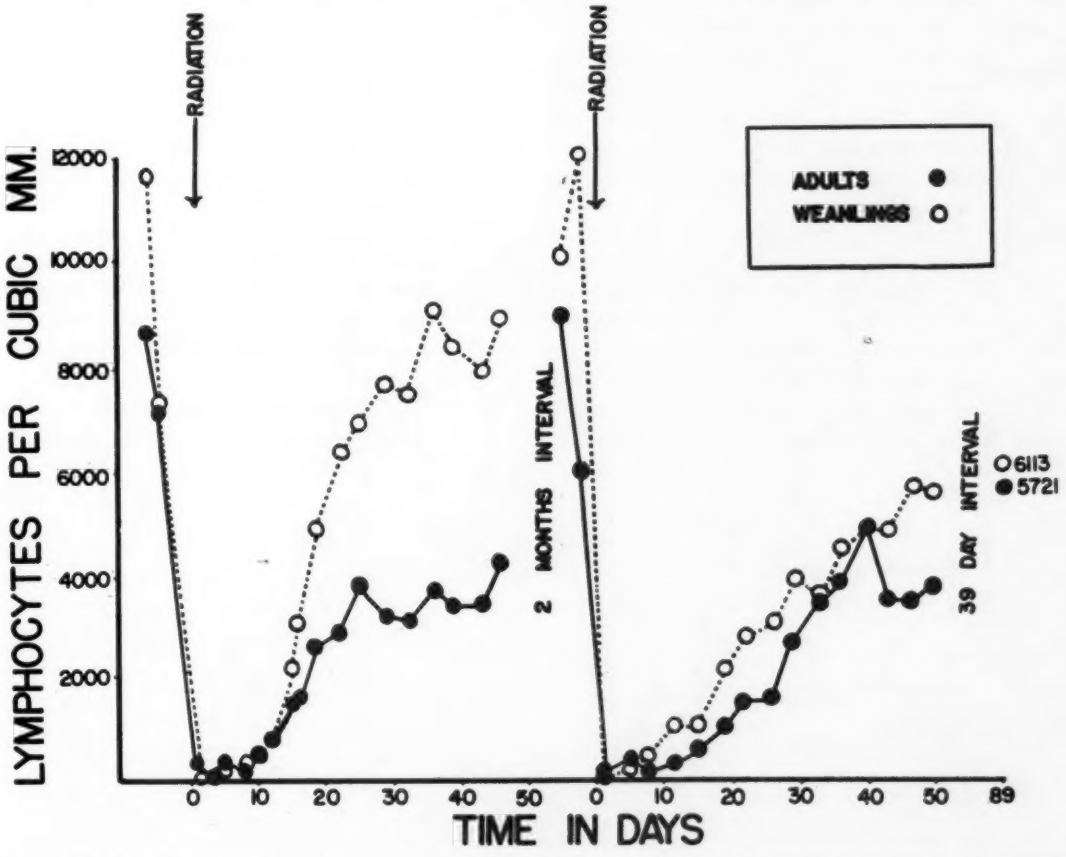

Fig. 2. Absolute Lymphocyte Count in Weanling and Adult Rats. The lymphocyte graph is very similar to that of the total leukocytes except that the adult rats never showed as good recovery following roentgen irradiation as did the weanlings. As long as the weanlings were young, they showed very good recovery, but upon attaining maturity their absolute lymphocyte count was quite similar to that of the adults. Lymphopenia followed roentgen irradiation in all rats. The weanlings, as weanlings, showed rapid recovery while the adults showed fair recovery only after one hundred and ten days of rest following the first exposure. The second exposure caused a permanent lymphopenia in all rats.

made a gradual recovery to 8,683 (58 per cent) by the fiftieth day and to 9,908 (66 per cent) by the termination of the experiment. Thus, there was incomplete recovery of the original weanling rats by one hundred and seventy-five days, following the two irradiation insults, with respect to the total leukocyte count.

(2) *Differential white blood cell count, relative values.*

a. *Lymphocytes:* These values are first presented as relative percentages of the total leukocyte count. Of all of the leukocytes, the control (preirradiated) weanlings had 72.8 per cent lymphocytes. One day following roentgen irradiation this value dropped to 4 per cent representing very severe lymphopenia. There was, however, a rather rapid recovery from this lymphopenia so that by eight days the lymphocytes represented 44 per cent of all of the leukocytes and by forty-six days they had recovered a normal level of 75.5 per cent.

Following two months' rest period the lymphocyte count was still normal, at 74 per cent. However, this value was quickly depressed by the re-exposure to 600 r roentgen rays and was found to be 9.3 per cent by twenty-four hours after exposure. Recovery was active by eight days when the count was 54 per cent and by fifty days it was 63 per cent. It did not rise to the normal of 73 per cent at any time, remaining at 62 per cent at the termination of the experiment. Thus, weanling rats never showed complete percentage-wise recovery from the radiation-induced lymphopenia.

b. *Neutrophils:* The number of neutrophils relative to the total number of leukocytes of the pre-irradiated weanling rats was 26 per cent. By twenty-four hours after roentgen irradiation with 600 r there was an increase in this relationship to 96 per cent. This represents a very high proportion of neutrophils. The value dropped gradually (73 per cent at eight days) until it reached 21 per cent at forty-six days.

The two months' rest period allowed recovery of neutrophils to 24 per cent of all of the leukocytes, which was quite normal. The re-irradiation again caused an increase, percentage-wise, of the neutrophils so that they represented 90 per cent of all leukocytes at twenty-four hours. This value dropped rapidly to 45 per cent by eight days and to 37 per cent by fifty days. At the termination of the experiment the relative value for neutrophils was 34 per cent which was somewhat higher than the original or control value of 26 per cent.

Here again, one must caution against erroneous interpretations of percentage

TABLE II

SUMMARY OF WHITE BLOOD CELL COUNTS
WEANLING RATS

Time	Total Leukocytes (Fig. 1)	Lymphocytes (Fig. 2)	Neutrophils (Fig. 3)
	Per Cent	Per Cent	Per Cent
Before Irradiation	14,540 (100)	10,614 (73)	3,926 (27)
1 Day After	1,900 (13)	76 (4)	1,824 (96)
8 Days After	1,780 (12)	445 (25)	1,299 (73)
46 Days After	11,970 (82)	9,097 (76)	2,514 (21)
	Two Months Rest Period		
Before Irradiation	14,940 (100)	11,056 (74)	3,735 (25)
1 Day After	2,508 (16.7)	226 (9)	2,257 (90)
8 Days After	1,083 (7.2)	585 (54)	487 (45)
50 Days After	8,683 (58)	5,470 (63)	3,213 (37)
84 Days After	10,333 (69)	6,303 (61)	3,927 (38)
86 Days After	9,908 (66)	6,143 (62)	3,369 (34)

values. The values given above for lymphocytes and neutrophils are both altered percentage-wise by roentgen irradiation, but not in the same direction in absolute terms. For instance, the percentage of neutrophils among all the leukocytes is greatly increased while their actual numbers in the blood stream is decreased.

To emphasize this dual analysis of the results, Table II is included which shows both absolute and relative (percentage) values. The absolute values are in terms of cells per cubic millimeter of whole blood while the percentages (in parentheses) relate always to the total white blood cell count as 100 per cent.

Table II gives the maximum depression of leukocytes at eight days post-irradiation, whether it is the first or the second exposure. Both the lymphocytes and neutrophils show similar drops, but they are not exactly parallel. The lymphocytes show the greatest effect (10,614 cells per cubic millimeter down to only 76) while the neutrophils show a drop from 3,925 to 1,299 in absolute count while exhibiting a rise from 27 per cent to 73 per cent in numbers relative to the total white blood cells. This simply means that there is greater loss among the lymphocytes. Following re-irradiation the absolute count of neutrophils dropped to the very low of 487

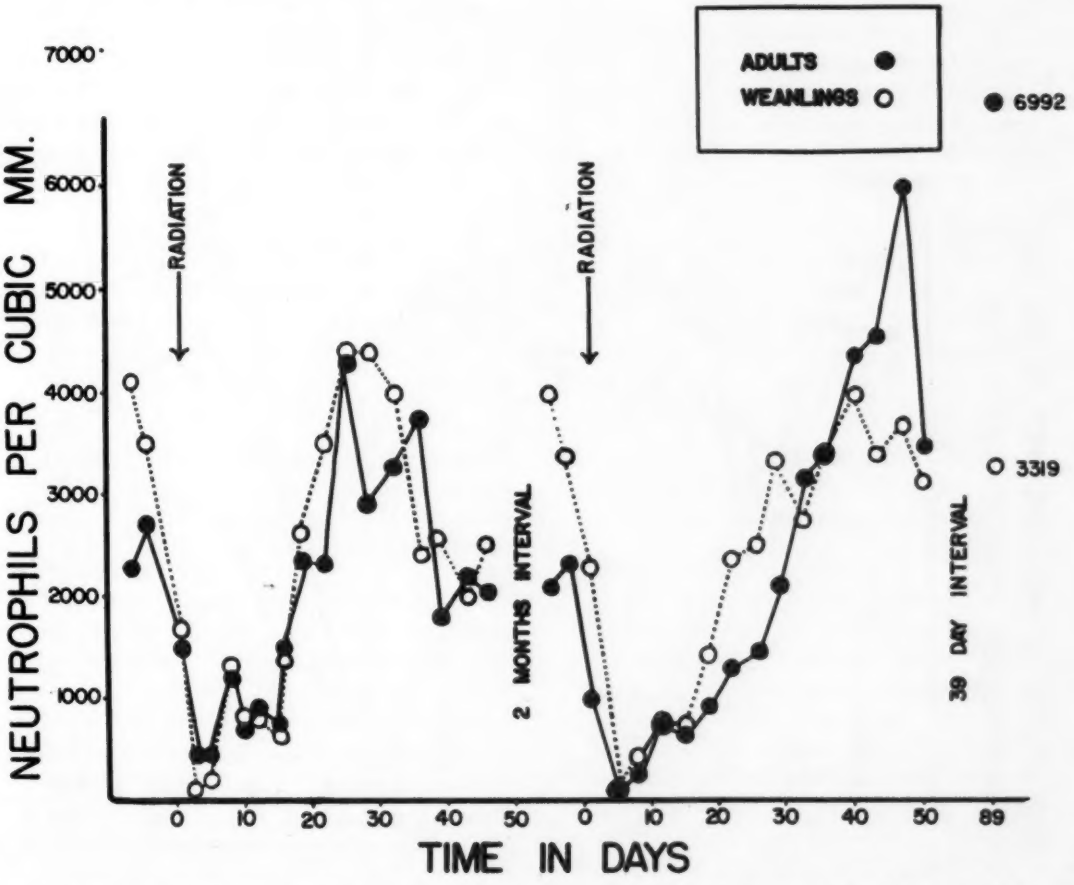

Fig. 3. Absolute Neutrophil Count in Weanling and Adult Rats. While the neutrophils of the weanlings were more abundant than those of the adults, they responded to roentgen irradiation with a greater drop than seen in the adults. Recovery was peculiar in that by twenty-five days the counts were at least normal in both adults and weanlings, but there was a subsequent depression in the count which was improved by the rest period only in the weanlings. Following re-irradiation the neutrophil count of the adults soared to about 6,000/cu. mm. and then dropped to normal. However, after thirty-nine days of rest the adult neutrophils again showed a great excess in absolute numbers, suggesting some dysfunction in neutrophil production.

cells, but these represented 45 per cent of all the leukocytes then present (Fig. 3).

(3) *Platelet count, absolute value* (Fig. 4).

The average number of platelets per cubic millimeter of whole blood of the pre-irradiated six week old weanling rats was 463,000. This number dropped slightly to 437,000 by twenty-four hours after roentgen irradiation with 600 r and to 15,000 by eight days. It gradually increased to 238,000 by the forty-sixth day after the initial exposure, representing about 51 per cent recovery. During this recovery period there was a time (at thirty-two days) when the count reached a high of 396,000 but it then dropped consistently, though slowly.

By the end of the two months' rest period, the platelet count was 373,000. The second roentgen exposure with 600 r at this time brought the count down to 41,000 by the eighth day and to 35,000 on the twelfth day from which there was gradual recovery to 370,000 by the fiftieth day. At the termination of the experiment the count had dropped 303,000 which was 81 per cent of the normal level. Since platelet count is inversely related to coagulation time, one might suggest that coagulation time is greatly increased by this roentgen irradiation and that the weanlings were permanently affected to a slight degree. It is doubtful whether the available methods of determining coagulation time would pick up such a small permanent increase.

B. *Erythrocytes, absolute value.*

(1) *Total red blood cell count.*

The pre-irradiation weanling rats had an average of 7.77 million red blood cells per cubic millimeter of blood. This is to be compared with 9.26 million for the adult controls. Roentgen irradiation caused a drop in the erythrocyte count, but the drop was not at all rapid. The first indication of a depres-

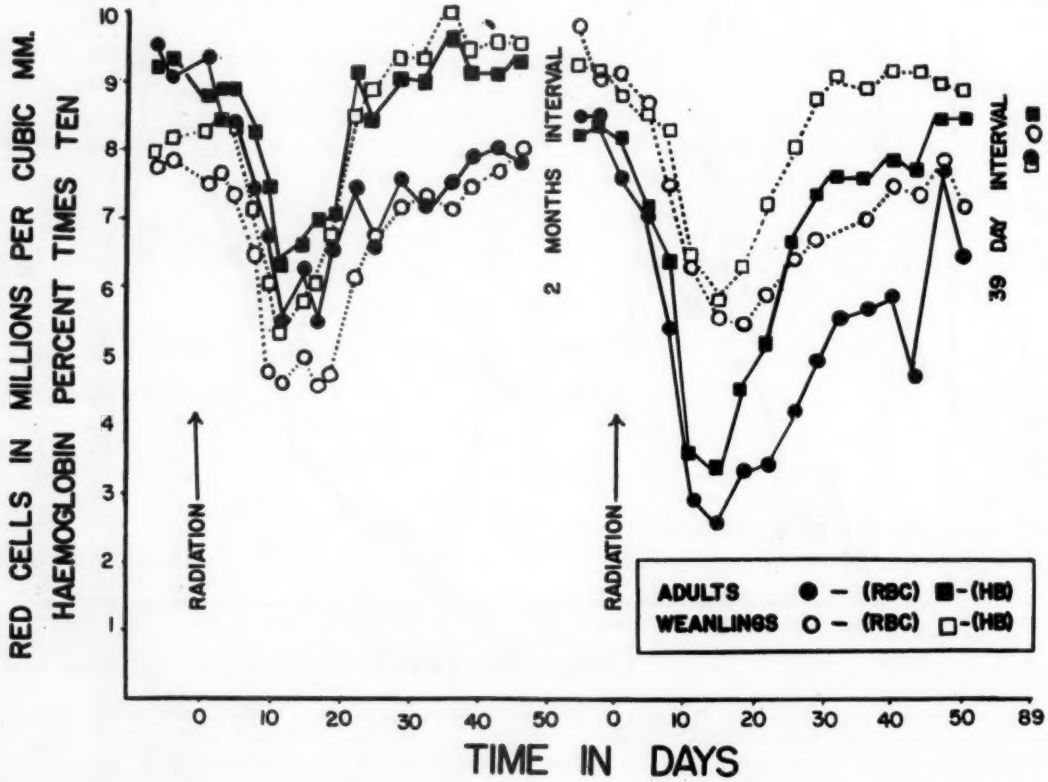

Fig. 4. Erythrocytes and Hemoglobin in Weanling and Adult Rats. In both of these categories the weanlings had lower counts and greater postradiation depression than did the adults but, following re-irradiation the situation was reversed. The final counts for all were quite normal, however.

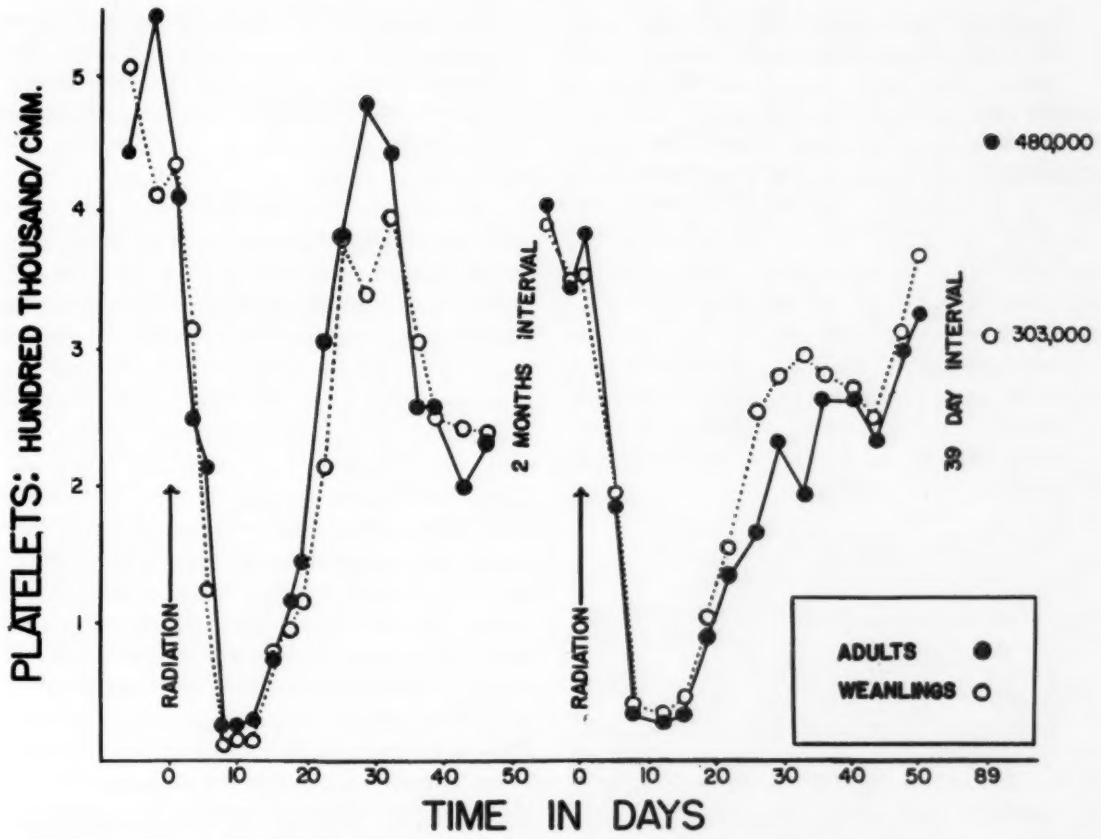

Fig. 5. Platelets in Weanling and Adult Rats. In this one graph there is no real difference in the response of the weanlings and adults following roentgen irradiation. The final adult count was considerably higher than that of the weanlings, but up to this point the curves are quite similar.

sion occurred at eight days and by the seventeenth day the count had dropped to 4.55 million. It then began to rise and reached 8.03 million, which is quite normal, by the forty-sixth day.

After two months of rest (and maturing) the original weanling rats were essentially like the adults and the erythrocyte count was 9.47 million. This suggests that the initial roentgen irradiation had little effect on the red blood cell count of the weanling but maturing rats.

Following the second 600 r whole body roentgen exposure, there was again a slow drop in the erythrocyte count, first noticeable by the fifth day and reaching the lowest level (5.59 million) on the nineteenth day. It then began to rise and reached 7.28 million by fifty days and 8.37 million by the termination of the experiment, at eighty-nine days. This latter figure suggests a rough 11 per cent drop in the red cell count (compared with the adult controls) which can be attributed to the roentgen irradiation. This is not considered of much significance.

(2) *Hemoglobin percentage.*

The pre-irradiated weanlings had an average of 80 per cent hemoglobin. This compared well with the adults which had both higher erythrocyte count and hemoglobin value (90 per cent).

Whole body roentgen irradiation with 600 r briefly and slightly elevated the hemoglobin value of the weanlings to 84 per cent on the third day, but this dropped slowly thereafter to a low of 53 per cent on the twelfth day. There followed a rather rapid recovery to 95 per cent by the forty-sixth day. This was higher than the level of the pre-irradiated weanlings and higher even than the pre-irradiated adults, suggesting slight overcompensation.

The rest period of two months did not

alter this value appreciably (92.6 per cent) and the re-irradiation did not have the same effect. The lowest value reached was 59 per cent on the fifteenth day and there was recovery to 90 per cent by the fiftieth day. At the termination of the experiment there was 88 per cent hemoglobin. There was evidence, therefore, of complete hemoglobin recovery.

C. *Abnormal Cell Types.*

There are two abnormal blood cell types to which one is always alert in irradiation studies. These are the nucleated erythrocytes which are immature cells, and the bilobed lymphocytes.

(1) *Nucleated erythrocytes.*

During the study all irradiated rats, both the adults and weanlings, possessed nucleated erythrocytes at some time after exposure. These abnormal cells appeared most frequently, and abundantly, on the seventeenth day after the first exposure. They never exceeded an average of 3.5 per smear. Following the second exposure to roentgen irradiation, there was a slightly higher incidence of these immature red blood cells in the adults (13/smear) than in the weanlings, but every rat had some. The greater number appeared on the fifteenth postirradiation day. By the termination of the experiment these abnormal erythrocyte cells had completely disappeared.

(2) *Lymphocytes with bilobed nuclei.*

Again, every irradiated rat, whether adult or weanling, exhibited some of these abnormal lymphocyte cells at some time after whole body exposure to 600 r. The percentage of the total number of lymphocytes which had bilobed nuclei was never very high but reached 3.58 per cent for the adults on the fifth day after exposure and 4.34 per cent for the weanlings on the tenth day. Some of these cells were present even at forty-six days after roentgen irradiation.

Following re-irradiation the adults seemed to exhibit a slightly higher incidence of lymphocytes with bilobed nuclei than did the weanlings with the highest value at 4.04 per cent on the eighth day. The weanlings had a high of 2.13 per cent on the fifteenth day. Some rats had these abnormal cells on the last day of the experiment, eighty-nine days after the second roentgen irradiation and one hundred and seventy-five days after beginning the study.

DISCUSSION

Stearner *et al.*[12] found overcompensation in the recovery of neutrophils in rats following 600 r whole body exposure and the lymphocytes returned to normal in thirty days. The erythrocytes never made full recovery even by three months after exposure. The next year Stearner,[13] studying only the adult rat, found that a second acute irradiation caused a greater anemia than did the first. Suter[14] exposed adult rats to 550 r and found the hemoglobin to fall in seven days and return to normal in from thirty to forty days. The platelets showed an initial rise and then a fall in the normal count in twenty-five days. The neutrophils were low at three days but rose in about eleven to twenty-five days. The lymphocytes showed a very rapid depression, followed by incomplete recovery in twenty-five days. Kirschbaum *et al.*[9] described leukemia in mice following roentgen irradiation. Ross *et al.*[10] attributed the postirradiation anemia to endothelial fragility and loss of erythrocytes into the lymph. Casarett,[3] in comparing the pathologic effects of irradiation of the weanling with the adult rats, included a study of the blood and found that the weanlings exhibited a greater depression in lymphocytes while the adults showed a greater reduction in the neutrophils. The dose used (800 r) did not permit recovery. Baum *et al.*[1] exposed male rats to 75 r gamma irradiation at seven day intervals but found that the hematopoietic regeneration, following irradiation, was so good that the maximum changes reflected only the effects of the last irradiation. Gershon-Cohen and Hermel[5] described leukocytosis occurring simultaneously with lymphopenia during the first few hours after exposure of rats to medium high doses of roentgen irradiation. At still higher levels of exposure there was a combined leuko-

penia and lymphopenia a few hours before death.

Schechmeister and Fishman[11] studied the effect of irradiation on leukocyte migration and found that the ability of the leukocytes to migrate did not return to normal until the twenty-first day after exposure.

Regarding the abnormal blood cells following roentgen irradiation, it was probably Dickie and Hempelmann[4] who first described the abnormal lymphocytes and correlated their frequency with the amount of exposure. Following this work Ingram and co-workers[6,7,8] described both the lymphocytes with bilobed nuclei and the nucleated erythrocytes in the blood of cyclotron workers but pointed out that both types of cells could be found in the blood of persons with certain infections. It was thought, at one time, that the mere occurrence of these abnormal lymphocytes could be taken as an indicator of radiation exposure and that their number might be correlated with the amount of exposure. This has not been confirmed. The most recent paper on this subject is by Bellack and Storer.[2]

SUMMARY

1. Weanling (six weeks old) and adult (six to nine months old) white rats of the Wistar strain were exposed to 600 r whole body roentgen irradiation and the blood constituents were analyzed for a period of forty-six days. There then followed a rest period of two months after which the rats were re-irradiated (600 r), and the blood constituents were again analyzed for an additional period of eighty-nine days. The reaction time and recovery rates of the various blood constituents were compared for the weanling and adult rats.

2. The *leukocyte* count for adult rats dropped to a low of 4.6 per cent by three days after roentgen irradiation while the weanlings responded by an even lower drop to 1.6 per cent on the third day. By forty-six days the adults had achieved recovery to 59 per cent and the weanlings to 82 per cent. *This indicated more rapid recovery of the weanlings.* After two months' rest, recovery for both weanling and adult rats was complete.

3. Following the re-irradiation at fifteen weeks, the adults again showed a drop in leukocytes to 4.6 per cent by the eighth day while the original weanlings, now matured, showed a drop to 7.24 per cent on the same day. By the termination of the experiment the adults had overshot their recovery to 140 per cent while the original weanlings had achieved only 66 per cent recovery. *This suggests permanent impairment of the mechanism for leukocyte production in the weanling rat and its stimulation (leukemia) in the adult.*

4. *Lymphopenia* developed in both the adult and weanling rats after roentgen irradiation reaching a low of 8.7 per cent (45 cells/cu. mm.) in the adult by the third day and of 4 per cent (76 cells/cu. mm.) in the weanlings by the first day after exposure. Recovery at forty-six days was 64 per cent in the adults and 76 per cent in the weanlings. These values are percentages of total leukocytes and when absolute values are given, *absolute recovery of lymphocytes is seen to be much better in the weanlings.* The adults recovered 51 per cent of their original total lymphocytes by forty-six days while the weanlings recovered 84 per cent.

5. Following the rest period of two months, the weanlings showed a slightly better recovery record of total lymphocytes than did the adults, although the percentage value with respect to total leukocytes was normal.

6. Following the second roentgen irradiation with 600 r at fifteen weeks, neither adult nor weanling showed the same degree of lymphopenia that they did previously. The adults dropped to 250 cells (20 per cent) while the weanlings, now mature, dropped to 226 cells (9 per cent) by the first day after exposure. The adults eventually possessed 68 per cent of their original number of lymphocytes while the weanlings reached 58 per cent. Recovery was about the same in both, neither achieving the normal level and thus *suggesting permanent*

damage to the mechanism of lymphocyte production in both weanling and adult rats.

7. The *neutrophils* showed almost a fourfold increase, following roentgen irradiation of either the weanling or adult rat with respect to percentage of total white blood cells. However, in absolute values the adults dropped from 2,695 cells to 470 cells (to 18 per cent) by three days and the weanlings dropped from 3,926 cells to only 1,299 cells (to 33 per cent) by eight days. Thus, the adults responded more quickly and radically than did the weanlings with respect to neutrophil destruction and loss.

8. Recovery of neutrophils to almost the normal level was achieved by both the weanlings and adults after two months of rest.

9. Re-irradiation brought the neutrophil count of adult rats down to 257 from 2,317 in eight days and down to 487 from 3,735 in the original weanlings, also in eight days. Thus, the original weanlings now responded more, as did the adults, by an extreme drop in the absolute neutrophil count. At the termination of the experiment the adult rats, twice irradiated, had three times as many neutrophils as originally while the weanlings were within the normal range. *Thus, the adults and not the weanlings gave evidence of damage to the mechanism of neutrophil-production, resulting in overproduction.*

10. The total *erythrocyte* count was initially higher for the adults (9.26 million/cu. mm.) than for the weanlings (7.77 million). Following whole body exposure to 600 r, both weanlings and adults dropped to the lowest red blood cell count on the seventeenth day, it being 5.47 million (59 per cent) for the adults and 4.55 million (58 per cent) for the weanlings. By forty-six days the weanlings had overshot their original count (to 8.03 million) and the adults were very slightly anemic (7.88 million).

11. A rest period of two months allowed some recovery in erythrocyte count on the part of the adults and further improvement for the weanlings so that their count (9.47 million) was normal for the adult stage which they had attained.

12. Following the re-irradiation with 600 r at fifteen weeks after the first exposure, the weanlings showed their maximum depression of erythrocytes at nineteen days (9.47 to 5.59 million) and the adults showed the greatest drop by fifteen days (8.56 to 2.63 million). By the time the experiment was terminated, the adults had not recovered, retaining a 24 per cent deficiency in red blood cells and proportional anemia. The weanlings, however, achieved 8.37 million red blood cells which was higher than their original value of 7.77 million but still short of the adult average of 9.26 million. Thus, *while the weanlings failed to achieve full erythrocyte recovery they did not show the same degree of anemia that was found in the adult rats.*

13. The original pre-irradiation *hemoglobin* was 80 per cent in the weanlings and 93 per cent in the adults. Both responded by a drop in these percentages with the lowest point at twelve days. The weanlings had 53 per cent and the adults 63.5 per cent. Both recovered well by forty-six days, the weanlings showing an increase over their original value and even over the adult controls. Following the re-irradiation the adults showed a larger drop (again at fifteen days) to 34 per cent while the weanlings dropped to only 59 per cent. Recovery was normal for both the weanlings and the adults by the termination of the experiment.

14. *Abnormal cell types:* Both nucleated erythrocytes and lymphocytes with bilobed nuclei were found at some time after whole body roentgen irradiation with 600 r in every rat examined, whether weanling or adult. The immature erythrocytes appeared most frequently and abundantly on the fifteenth day after exposure, in both weanlings and adults. This was about the time of lowest erythrocyte count. Following the second exposure the incidence of nucleated red blood cells was slightly higher than after the first exposure, again reaching a maximum on the fifteenth day. None was

present at the termination of the experiment.

The lymphocytes with bilobed nuclei never were more than 3.6 per cent of all of the lymphocytes, but this level was reached five days after the adults received irradiation to 600 r. In the weanlings the peak was 4.34 per cent on the tenth day. These peaks occurred several days after the maximum lymphopenia. Some of these cells were present at forty-six days, and some rats had such abnormal lymphocyte cells at the termination of the experiment (one hundred and seventy-five days after the initial exposure).

CONCLUSIONS

Weanling rats responded more quickly and more drastically to whole body roentgen irradiation by leukopenia than did the adults, but they also recovered better after the first irradiation insult. Following the second exposure the adults recovered to 140 per cent, showing some leukocytosis (leukemia?) while the weanlings recovered only to 66 per cent (leukopenia). In either case there appeared to be permanent damage to the leukogenic processes.

Lymphopenia occurred by the first day in the weanlings and by the third day in the adults and was roughly equivalent. Recovery in absolute values was 84 per cent in the weanlings and 51 per cent in the adults. The second exposure was not followed by the same degree of lymphopenia for either the weanling or adult. Neither was able to achieve normal lymphocyte recovery, suggesting permanent damage to the mechanism of lymphocyte production (lymphopenia).

Adult rats lost a higher percentage of their neutrophils (82 per cent loss) by eight days than did the weanlings (67 per cent loss), but recovery was quite complete in both by forty-six days. The second exposure, occurring at a time when the weanlings were fifteen weeks older, caused little difference between the adults and the matured "weanlings" with respect to neutrophil reaction. However, recovery brought the adults to a level 3 times higher than the original normal count while the weanlings recovered to the normal range.

Erythropenia occurred in both weanlings and adults by the seventeenth day with a red blood cell drop of 42 per cent for the weanlings and 41 per cent for the adults. The weanlings showed better recovery. The second exposure caused the greatest drop in red blood cells of the adults (to 30 per cent) in fifteen days while the weanlings dropped to only 59 per cent in seventeen days. The adults recovered fully from their irradiation-induced anemia, while the weanlings eventually reached a level normal for control adults.

The hemoglobin was originally lower in the weanling than in the adult and both responded to whole body roentgen irradiation with a maximum drop at twelve days. The weanlings showed the slightly greater drop (to 53 per cent) than did the adults (to 63 per cent). The re-irradiation caused a much greater drop in adult than in weanling hemoglobin, but recovery was normal for both by the termination of the experiment.

Abnormal nucleated erythrocytes and lymphocytes with bilobed nuclei were found at some time in every irradiated rat, whether weanling or adult. The nucleated erythrocytes were at their peak on the fifteenth day for both the weanling and adult rats, but none was present at the termination of the experiment. The lymphocytes with bilobed nuclei were never more than 4.34 per cent (tenth day), but some were present in some rats at the termination of the experiment, after one hundred and seventy-five days.

Dr. Roberts Rugh
Department of Radiology
College of Physicians and Surgeons
Columbia University
New York 32, New York

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EDITORIALS

THE RELATIVE BIOLOGICAL EFFECTIVENESS OF SUPERVOLTAGE RADIATIONS

SOME thirty years ago Lauritsen and Bennett[12] described the design of a supervoltage roentgen-ray tube for potentials of "600 kv. or higher." This tube was put into operation shortly thereafter by Mudd and his associates at the California Institute of Technology, and the clinical experience of this group with the treatment of almost 300 patients was published a few years later.[14] These authors reported that with the 600 kv. unit, and filtration of 5 mm. steel plus 2 mm. aluminum, it required about 950 r to produce a threshold erythema; with 200 kv. and filtration of 0.5 mm. copper plus 2 mm. aluminum it required about 550 r. In other words, the relative biological effectiveness (RBE) of the supervoltage unit in terms of human erythema production, was about 0.6.

During the decades which have followed the publication of that paper, there has been considerable discussion regarding the relative biological effectiveness of orthovoltage (200 to 300 kv. peak) and supervoltage (600 to 2,000 kv. peak) radiations. The former is usually filtered to give a half-value layer of from 0.5 to 2 mm. copper, and the latter filtered or designed to give a half-value layer of from 5 to 15 mm. copper. The matter is of importance in connection with the adequate treatment of deep-seated tumors, especially when higher energy equipment is employed. If the above difference in erythema production is paralleled by difference in squamous cell lethality, it is obvious that significantly larger doses of supervoltage radiation must be given in order to equate the effects of orthovoltage therapy.

It has been the clinical experience of many therapists that the biological effectiveness of those supervoltage rays which have been available for almost sixty years (gamma rays from radium) is unquestionably less than that of orthovoltage rays. For example, in treating squamous cell carcinoma of the cervix uteri with gamma rays, it has been and still is estimated that a dose of about 9,000 r_γ is necessary to equate the cancerocidal reaction produced by a dose of 6,000 r with orthovoltage roentgen rays (RBE 0.66).

A large number of experimental procedures have been devised and carried out in an attempt further to elucidate this question. Most of these procedures have involved acute or whole-body irradiation, with measurements of early biological changes, rather than chronic or late results in terms of cell destruction. They are, therefore, not strictly comparable with the aims and results of long term irradiation as commonly employed in the treatment of human cancer. Based on some of these experiments, certain clinicians and physicists have concluded that *when properly measured*, the biological effect of radiation with orthovoltage or supervoltage beams is the same; that is, the RBE is unity. On the other hand, it continues to be the clinical experience of most radiotherapists that there is a significant difference. For this reason, it may be of interest to review some of the more recent literature and reports dealing with this problem.

Chase *et al.*[5] measured the degree of graying of the hair of mice and found that 20 mev. roentgen rays had 0.7 the effectiveness of 200 kv. roentgen rays (half-value layer 0.34 Cu). Ting *et al.*[17] recorded the leukocyte count of the peripheral blood of 3 different strains of mice, and found that

in order to obtain 75 per cent leukocyte reduction, the relative biological effectiveness of 23 mev. betatron rays and 200 kv. roentgen rays was 0.65. Austin *et al.*[2] used the graying of the hair of mice, and noted that 17 mev. electrons had 0.6 the effectiveness of 150 kv. roentgen rays (half-value layer 0.15 Cu). Bateman[3] measured the induction of dominant lethals in Drosophila and found that 4 mev. linear accelerator roentgen rays had a relative biological effectiveness of 0.84 as compared to 300 kv. roentgen rays. Moos *et al.*[13] studied the effects on survival rate and/or pathological changes in tissues of rats, and found that the relative biological effectiveness of 22 mev. roentgen rays was 0.6 compared to 400 kv. roentgen rays. Kohn and Gunter[10] used 4 tests to determine the relative biological effectiveness of 1,000 kv. roentgen rays and 250 kv. roentgen rays; the 4 tests were: (a) the dose survival curves for a haploid strain of yeast, (b) the LD_{50} for adult mice, (c) the dose response curve for testicular weight in mice, and (d) the LD_{50} for the four day old chick embryo. The relative biological effectiveness of the two beams ranged from 0.82 to 0.88. They commented that Boland found the relative biological effectiveness of a 4 mev. linear accelerator compared to 250 kv. roentgen rays to be about 0.87 and, therefore, concluded that the relative biological effectiveness of 1,000 kv. peak roentgen rays and 4 mev. linear accelerator rays was similar. Upton *et al.*[18] investigated the effects of single whole-body doses on mice. They found that the biological effectiveness relative to 250 kv. peak roentgen rays was 0.7 for radiocobalt gamma rays and 1.4 for cyclotron produced fast neutrons.

Storer *et al.*[16] made a very extensive series of experiments comparing the relative biological effectiveness of *nine* different types of beams or radiations, including 250 kv. peak roentgen rays, 1.2 mev. gamma rays from cobalt 60, 4 mev. gamma rays, 14 mev. neutrons, 60 kev. beta particles from tritium, fission neutrons, thermal neutrons, alpha particles and fission fragments. Using mice, they made lethality studies, splenic and thymic atrophy studies, testicular atrophy studies, and body weight loss studies. Based on thirty day mouse lethality observations, they found that the relative biological effectiveness was as follows: 250 kv. roentgen rays, 1.00; 1–2 mev. (radium or cobalt) gamma rays, 0.77; 4 mev. gamma rays, 0.54. They also quoted some human investigations in which skin damage was the biologic test system. When single acute doses were employed and short term effects measured, the relative biological effectiveness was 1.00 for 250 kv. roentgen rays and 0.77 for gamma rays from radium or cobalt. Bora[4] reported two sets of experiments using Tradescantia bracteata microspores. He found that the relative biological effectiveness of megavoltage or gamma rays was approximately 0.7 as compared to 220 kv. roentgen rays.

Most of the above investigations involved relatively acute doses and rather short latent periods for the evaluation of results. As previously noted, in dealing with human cancer, protracted treatment is often employed and weeks or months elapse prior to evaluation of the biological effect. Despite this wide difference in dose rate and the intervals utilized for determination of radiation effects, it is of interest to note that the experiments disclose an average relative biological effectiveness of about 0.7 in comparing supervoltage rays and orthovoltage (250 kv.) roentgen rays.

Garcia[9] observed that in the treatment of cancer of the human cervix, equal biologic changes in equal numbers of days required that the dose of gamma rays be about 50 per cent greater than the dose of roentgen rays. Accordingly, in calculating the total doses delivered to the female pelvis, he multiplied his gamma ray doses by a correction factor of 0.67 before adding them to the roentgen-ray dosage as measured in roentgens. A closely similar factor (0.69) is used at the Marie Curie Hospital in London. Ellis,[8] on the basis of extensive clinical experience with visceral and cu-

taneous cancer in humans and the studies of L. Cohen, reported the relative biological effectiveness of gamma rays to 200 kv. roentgen rays as 0.7. Allen,[1] who has had extensive clinical experience with 250 kv. roentgen rays, 400 kv. roentgen rays, 1,000 kv. roentgen rays and a radiocobalt unit, believes that the relative biological effectiveness of the gamma rays or supervoltage roentgen rays (compared to the 200 kv. roentgen rays) is about 0.65. Lanier,[11] who has had some clinical experience with various qualities of radiation and in whose laboratory considerable research is being conducted on this question of relative biological effectiveness, believes that the order is approximately as follows: 200 kv. roentgen rays 1.0, gamma rays from radium 0.7, 1,000 kv. roentgen rays 0.8.

Paterson,[15] after careful animal and human investigations, concluded that the relative biological effectiveness of 4 mev. roentgen rays compared to 300 kv. roentgen rays lay in the range of 0.74 to 0.96. He considered the median figure to be about 0.85.

Finally, Devine *et al.*,[7] after several years' experience with cobalt teletherapy of malignant nasopharyngeal lesions, concluded that "when supervoltage therapy is used it is necessary to increase by a third the dose that we would have used with conventional therapy"—a relative biological effectiveness for cobalt of 0.75.

The doses mentioned in the opening paragraph are given in roentgens, and include both estimated and measured roentgens in the soft tissues. A more precise term for the latter is *rads*. It is believed that in the energy range from 200 kv. to 1 mev., a dose of 1,000 roentgens is approximately equal to 960 rads in *soft tissues*. In other words, the tissue roentgen and the rad essentially are interchangeable insofar as intensive protracted irradiation doses to soft tissues are concerned. This is not the case when doses to compact bone, or doses in the low voltage range (50 to 180 kv.), are considered.

All in all, the relative biological effectiveness (in terms of clinical response and human cancer cell destruction) of supervoltage rays as compared to orthovoltage rays is about 0.75. This ratio applies to soft-tissue lesions, notably epidermoid carcinoma. Larger doses of supervoltage rays must, therefore, be given if it is desired to produce cancerocidal effects comparable to those attainable with orthovoltage rays. This fact is almost uniformly confirmed by those reporting clinical experience with radiation therapy of human cancer. The lower relative biological effectiveness is presumably an important element in the increased tolerance of equivalent physical doses of supervoltage rays.

L. HENRY GARLAND, M.D.

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ERRATUM

The authors of the article *Hypophosphatasia*, which was published in the September, 1957 issue of the American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, "would like to amend a serious error in the first word of the summary which is given as 'Hypercalcemia,' whereas, of course, it should read 'Hypophosphatasia'."

BYRL RAYMOND KIRKLIN, M.D.
1888–1957

ON March 2, 1957, death closed the notable career of one of America's most distinguished and most beloved radiologists. The end came quickly after a brief illness, as he would have wished it to be; with dignity and quiet grace, as he would have planned it had that been possible.

Byrl Raymond Kirklin, son of John Walter and Sarah McCreery Kirklin, was born at Gaston, Indiana, on September 22, 1888. Indiana University conferred on him the degree of doctor of medicine in June, 1914. In 1927 he received the degree of bachelor of science from the same institution. He was married to Miss Gladys Marie

Webster, on June 3, 1915, just after he had completed his internship in the Protestant Deaconess Hospital in Indianapolis.

While he was an intern he manifested a special interest in urology and urologic surgery. To gain more knowledge and experience in this field he accepted the position of resident physician in the Home Hospital in Muncie, the metropolis and county seat of his home county in Indiana. New x-ray equipment recently had been installed in this hospital, and he was made responsible for it. Such an environment was provocative to the young physician, and a lively interest in radiology was soon awakened in him. He devoted himself to mastering every detail of the use of the then new and unfamiliar tool of medicine, and by 1917 he felt competent enough to limit his professional activities to that field. Accordingly, early in that year, he opened an office in Muncie for the private practice of radiology.

Then World War I broke out. Dr. Kirklin volunteered for service in August, 1917, and was at once commissioned a first lieutenant in the Army Medical Corps. Soon he found himself an instructor in the Army School of Roentgenology in Fort Riley, Kansas. He completed his military service in World War I as chief roentgenologist at the United States Army General Hospital at Fort Bayard, New Mexico.

Dr. Kirklin returned to Muncie in February, 1919, to resume the private practice he had only just established 18 months before.

The intensive experience and intimate acquaintance with radiologic problems which he gained during his tenure in military service removed all doubts from Dr. Kirklin's mind about radiology as a career. Afire with interest in and enthusiasm for the rapidly expanding applications of the roentgen rays and radium to medical diagnosis and treatment, he read avidly, attended medical meetings at every opportunity, liberally invested both time and income in visits to other radiologists nearby and far away, and then applied with characteristic ingenuity, imagination, and skill the new things he learned to his growing practice in the relatively small community which was his home.

Recognition came quickly. He had ability, a deep-seated sympathy for the sick, a co-operative spirit already then highly developed and a gracious and cordial friendliness. Soon he was elected president of the staff of the Home Hospital of Muncie, and a little later he became president of the Academy of Medicine of Muncie—high honors, certainly, for a very young man in a very young specialty of medicine. In 1919 he was elected to membership in the American Roentgen Ray Society, the medical society he was to cherish above all others for the rest of his days.

By 1921 he had published a few papers on roentgenologic subjects, and was gathering material for others. Having observed at first hand the exemplary work of his good friend and former superior officer in military roentgenology, Dr. Ariel W. George, he became convinced that thoughtfully planned and carefully conducted roentgenologic examinations could be made to contribute effectively to an improved diagnosis of disease of the gallbladder, even in the absence of demonstrable cholelithiasis. At this time there was as yet no hint of the cholecystographic contrast media, but the clinical problem posed by the disease was one of everyday occurrence, often obscure and frustrating. In those days the roentgenologic approach was comparatively complex and time-consuming; it required a most scrupulous roentgenographic technique, and a certain amount of critical fluoroscopic observation.

The problem became a special project for the inquisitive energies of the young radiologist, Kirklin. The subject itself was being discussed extensively wherever radiologists gathered. He took an active part in these debates, both with contributions of his own and with formal and informal evaluations of papers prepared by others. Before long he was recognized as one of the experts in this field of roentgenologic diagnosis.

Opportunities for him to enter practice

in metropolitan centers began to unfold. Several medical schools made overt bids for his services in organizing or taking over the direction of departments of radiology. These were alluring prospects, and he considered some of them most thoughtfully. In 1922, much to the young man's surprise and gratification, Dr. William J. Mayo invited him to spend some time in Rochester, there to demonstrate his methods of bringing the gallbladder under roentgenologic scrutiny, and to amplify his concepts and procedures, if possible, by use of the more extensive clinical material and other facilities of the Mayo Clinic. This invitation certainly was of the nature of an accolade, as well as an unusual and attractive opportunity, but Dr. Kirklin characteristically perceived that it also constituted an exacting assignment which would require tact and firmness of purpose. He was only 34 years old at the time, and had been practicing radiology for a relatively short time in a small community; yet he had been called upon to present his techniques and to introduce his ideas into the department headed by the nationally recognized Russell D. Carman! Dr. Kirklin had become acquainted with Carman and Alexander B. Moore and Charles G. Sutherland in previous visits to Rochester and from association with them at meetings of radiologists. All of them had been very friendly to him, and as a consequence the genuine anxiety produced by the invitation of Dr. Mayo was relieved, to some degree.

The summer Dr. Kirklin spent in Rochester in 1922 proved to be interesting and stimulating. Actually, the work on roentgenography of the gallbladder which he demonstrated was received with polite interest, but without much enthusiasm. Eventually, however, the time he spent in Rochester in 1922 at considerable personal sacrifice was to influence in a remarkable way Kirklin's inevitable progress toward the prestige which ultimately came to him. With his ready facility for making friends and keeping them, and the conviction and pertinacity with which he developed and argued his thesis that roentgenologic methods could be made to reveal reliable evidence of significant disease of the gallbladder often enough to make the procedure an integral part of the clinical investigation, he made an enduring impression of his worth on many members of the staff of the Mayo Clinic.

In the fall of 1925, it became known that Dr. Carman had been stricken with a fatal illness. On May 1, 1926, six weeks before the death of that distinguished figure in American roentgenology, the name of Dr. B. R. Kirklin was on the roll of the staff of the Mayo Clinic as a consultant in roentgenology. In January, 1930, he was named head of the Section of Diagnostic Roentgenology. Meanwhile, he had become an instructor in radiology in the Mayo Foundation, Graduate School, University of Minnesota, in 1927. He was advanced to assistant professor in 1930 and associate professor in 1933, and in 1936 he was made professor of radiology, the academic rank he held until his retirement in 1953.

In the ensuing years additional honors, and with them new responsibilities, came to Dr. Kirklin at an accelerated rate. The routine work in his department was increasing day by day; gradually his staff, both lay and professional, had to be enlarged; the physical facilities had to be expanded several times; equipment had to be modified and kept up to date; more and more applications for fellowships in radiology under his direction were being received and accepted. He kept his hand in all these activities, but in addition maintained the will and the drive to develop a large bibliography of his own and in collaboration with others, to maintain an unusually active schedule as speaker at medical meetings in all parts of the country, and to function, always with efficiency and distinction, in many positions of responsibility in a variety of medical organizations. He found time for recreation, too. Many will remember him as a most agreeable, fun-loving, considerate companion both in travel and in sport. Obviously, his talent

for organization and for husbanding his own time and energy was unusually great.

Dr. Kirklin was one of the elected group of eminent radiologists who founded and guided the destinies of the American Board of Radiology. Many will hold that his greatest contribution to medicine in general and to radiology in particular was based upon this activity. He was secretary-treasurer of the Board from the time of its incorporation in 1934 until he died. It was entirely natural, then, that he should proceed to the Advisory Board for Medical Specialties, established in 1934 as a result of stimulus from the American Medical Association and other interested groups. He served as secretary-treasurer of this Board for many years. These were arduous and time-consuming activities. He was deeply devoted to them, and seemed to derive much satisfaction from the services he provided so well and so generously.

Early in May, 1943, Dr. Kirklin once again volunteered for service in the Medical Corps of the Army of the United States. He was at once accepted, and was given the grade of colonel. He served as chief consultant in radiology to the Surgeon General of the Army. How well he served in this capacity is recorded chiefly in the hearts and memories of the radiologists and other physicians in military service in World War II. By direction of the Secretary of War, he was authorized to wear the Army Commendation Ribbon, a distinction which his labors certainly entitled him to enjoy. He was released to civilian life on December 27, 1945.

Dr. Kirklin was a fellow of the American Medical Association. In 1936 he was elected chairman of the Section on Radiology of the American Medical Association, and in 1946 he was elected a member of the House of Delegates of that association. In 1948 he was chosen to be a member of the American Medical Association's Council on National Emergency Medical Service, and of its Joint Committee for Hospital and Residency Approval. The American Roentgen Ray Society honored him with its presidency in 1936; in 1946 it made him its Caldwell Lecturer. In 1939, under the direction of the president-elect of the American Roentgen Ray Society of that year, Dr. Edward L. Jenkinson, Dr. Kirklin organized the Section on Instruction of that Society, a section that since has been a regular feature of the annual sessions. Until 1948 Dr. Kirklin was director of this section. He was a fellow of the American College of Radiology, and served as president of the college in 1945. He was a fellow of the American College of Physicians, a member of the Radiological Society of North America, of the American Gastroenterological Association, of the Central Society for Clinical Research, of the International Congress of Radiology, of the Association of Railway Surgeons, of the Minnesota State Medical Association, the Olmsted County Medical Society, the Southern Minnesota Medical Association, the Minnesota Trudeau Society, the Academy of Medicine of Muncie, the Alumni Association of the Mayo Foundation, the Sigma Chi academic fraternity, the Phi Rho Sigma medical fraternity, the Society of the Sigma Xi, and of Rotary International. In 1929 he and Dr. Leo G. Rigler established the Minnesota Radiological Society. Dr. Kirklin was the second president of this Society, serving in 1930.

He was a corresponding member of the Academía Nacional de Medicína de Colombia, and of the Sociedad Venezuelana de Radiología.

Honorary memberships in foreign and domestic medical societies came to Dr. Kirklin in profusion: the Sociedad Colombiana de Radiología, the Sociedad Radiológica y Fisioterapéutica de Cuba, Sociedad Mexicana de Radiología y Fisioterapía, Sociedad Radiológica Panameña, Association of Gastroenterologists of Paris (France), Royal Society of Medicine of London, Deutsche Röntgengesellschaft, Detroit Roentgen Ray and Radium Society, Mississippi Valley Medical Society, St. Louis Medical Society, Chicago Roentgen Ray Society, Dallas Southern Clinical

Society and the International College of Surgeons.

Since 1946 Dr. Kirklin had been a member of the advisory board of the *Bulletin of the U. S. Army Medical Department;* he was a member of the editorial boards of *Gastroenterology* and of the AMERICAN JOURNAL OF ROENTGENOLOGY, RADIUM THERAPY AND NUCLEAR MEDICINE. From 1950 onward he was chairman of the Minnesota State Advisory Committee to Selective Service. In Rochester, he had been president of the local club of Rotary International, and a member of the board of directors and later president of the Rochester Golf and Country Club.

Dr. Kirklin is survived by his wife, Mrs. Gladys Webster Kirklin; a son, Dr. John W. Kirklin, head of a section of surgery in the Mayo Clinic; a daughter, Mary W. (Mrs. Karl J. Ladner, of Rochester); a sister, Mrs. Arthur Saint, of Newcastle, Indiana; three brothers, Wayne Kirklin, of Muncie, Indiana; Floyd Kirklin, of Rushville, Indiana; and Dr. Oren L. Kirklin, of Indianapolis, Indiana.

Here was a life replete with activity and achievement. The remarkable feature of it is not that so much was accomplished in so many fields, but that the achievements were realized with the accompaniment of so genial a manner and such apparent equanimity. Like most of us, Dr. Kirklin had his own moments of dejection and weariness of the vicissitudes of life, but his self-control was developed so highly that one had to know him very well to be able to detect the very occasional minor manifestations of agitation or restiveness in him. His was not the equanimity of a cold, disinterested temperament, but rather, that based on a well-ordered self-discipline.

There was an amiable, entirely admirable fastidiousness about him, manifest in his work, his person and in the implements of his work and recreation. Even though he was engaged in so many diverse activities, he possessed the enviable ability to concentrate on one problem at a time, to appraise it accurately and judiciously and to dispose of it and then to take up another problem, never impetuously but always deliberately. Despite his unfailing good nature, he was not a man to avoid the unpleasant or the difficult. When he felt himself harassed he sought the counsel of others. He was realistic enough to put his trust in facts as he saw them, and dispassionate enough to make his judgments of men with composure and restraint.

All who knew him admired his warm friendliness. He had a ready grace in meeting strangers and a rare gift of putting them at ease promptly, but there was also a quiet, natural dignity about him which was unmistakable without being quite palpable. Rancor and discord among men were abhorrent to him; he met such distasteful incidents by a skillful restoration of amity and concord, often resolving disharmonies by bringing his own understanding and instinctive sense of justice into the situation, proceeding to equitable compromise when principles and high ideals would not be jeopardized by such a solution.

Dr. Kirklin's life was happy with satisfactions. His family life was exemplary in every way. He lived to see two fine children grow to adulthood, vigorous and purposeful, well on their way in productive and satisfying careers. He lived to see the heritage of his notable work reflected in the men he had taught and inspired and sent forth enabled to minister more effectively to the sick, accepting, practicing and promulgating further abroad the ideals and principles he himself was instrumental in formulating.

His friend and collaborator, Albert Miller, wrote of Russell D. Carman: "The world of x-ray has lost a master workman. For a time it will grieve that he is dead. For a longer time it will rejoice that he lived." Surely, Kirk's life and work were fashioned to such massive proportions as to warrant such a final tribute. Men of medicine all over the world know how well he succeeded.

HARRY M. WEBER, M.D.

SOCIETY PROCEEDINGS AND NEWS ITEMS

MEETINGS OF RADIOLOGICAL SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. Barton R. Young, Germantown Hospital, Philadelphia 44, Pa. Annual meeting: Shoreham Hotel, Washington, D. C., Sept. 30–Oct. 3, 1958.

American Radium Society
Secretary, Dr. Theodore R. Miller, 139 East 36th St., New York 16, N. Y. Annual meeting: Hollywood Beach Hotel, Hollywood Beach, Fla., March 27–29, 1958.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y. Annual meeting: Palmer House, Chicago, Ill., Nov. 17–22, 1957.

American College of Radiology
Executive Secretary, William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill. Annual meeting: To be announced.

Section on Radiology, American Medical Association
Secretary, Dr. T. Leucutia, Harper Hospital, Detroit 1, Mich. Annual meeting: June 23–27, 1958, San Francisco, Calif.

American Board of Radiology
Secretary, Dr. H. Dabney Kerr. Correspondence should be directed to Kahler Hotel Building, Rochester, Minn. The deadline for filing applications for the Spring 1958 examinations is Jan. 1, 1958. Meeting and Examinations May 19–23, inclusive, Palmer House, Chicago, Ill.

Ninth International Congress of Radiology
Secretary-General, Dr. Hans v. Braunbehrens. Request for information should be addressed to Dr. Viktor Loeck, Kongressbüro, Forsthausstrasse 76, Frankfurt am Main, Germany. Annual meeting: Munich, Germany, July 23 to July 30, 1959.

Sixth Inter-American Congress of Radiology
Secretary for North America, Dr. Jorge de la Feor, Hospital Arzobispo Loayzo, Lima, Peru. Meets in Lima, Peru, Nov. 2–8, 1958.

Alabama Radiological Society
Secretary, Dr. J. A. Meadows, Jr., Medical Arts Bldg., Birmingham 5, Ala. Meets time and place Alabama State Medical Association.

American Nuclear Society
Executive-Secretary, Dr. W. W. Grigorieff, P.O. Box 963, Oak Ridge, Tenn.

Arizona Radiological Society
Secretary, Dr. R. Lee Foster, 1313 N. Second St., Phoenix, Ariz. Two regular meetings a year. Annual meeting at time and place of State Medical Association and interim meeting six months later.

Arkansas Radiological Society
Secretary, Dr. E. A. Mendelsohn, Holt-Krock Clinic, Fort Smith, Ark. Meets every three months and also at time and place of State Medical Association.

Association of University Radiologists
Secretary, Dr Paul Riemenschneider, Medical College, State University of New York, Syracuse, N Y.

Atlanta Radiological Society
Secretary, Dr. Luther Clements, 35 Linden Ave., N.E., Atlanta, Ga. Meets monthly, except during three summer months, on second Friday evening.

Blockly Radiological Society
Secretary, Dr. Samuel Finkelman, 101 S. Twentieth St., Philadelphia, Pa.

Brooklyn Radiological Society
Secretary, Dr. Harold N. Schwinger, 62 8th Ave., Brooklyn, N. Y. Meets first Thursday of each month October through May.

Buffalo Radiological Society
Secretary, Dr. Charles Bernstein, 685 Delaware Ave., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Roentgen Ray Society
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse, N. Y. Meets January, May, November.

Central Ohio Radiological Society
Secretary, Dr. Arthur R. Cohen, 41 S. Grant Ave., Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, November, January, March and May at Fort Hayes Hotel, Columbus, Ohio.

Central Society of Nuclear Medicine
Secretary, Dr. Robert S. Landauer, Radiation Center Building, 1903 West Harrison St., Chicago 12, Ill.

Chicago Roentgen Society
Secretary, Dr. Arthur S. J. Petersen, 11406 Parnell Ave., Chicago 28, Ill. Meets second Thursday of each month, October to April inclusive at the Sheraton Hotel at 8:00 P.M.

Cleveland Radiological Society
Secretary, Dr. Frederick A. Rose, 2065 Adelbert Rd., Cleveland 6, Ohio. Meetings at 7:00 P.M. on fourth Monday of each month from October to April at Tudor Arms Hotel.

Colorado Radiological Society
Secretary, Dr. Lorenz R. Wurtzebach, 601 Nineteenth Ave., Denver, Colo. Meets third Friday of each month at Denver Athletic Club.

Connecticut Valley Radiologic Society
Secretary, Dr. T. J. Crowe, 53 Center St., Northampton, Mass. Meets second Friday October and April.

Dallas-Fort Worth Radiological Club
Secretary, Dr. A. H. Keene, 3707 Gaston Ave., Dallas, Texas. Meets monthly, third Monday, at Greater Fort Worth International Airport at 6:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. Joseph O. Reed, Jr., Harper Hospital, Detroit, Mich. Meets monthly first Thursday, October through May, at David Whitney House, 4421 Woodward Ave., at 6:30 P.M.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434 30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

Florida Radiological Society
Secretary, Dr. C. Robert DeArmas 135 Broadway, Daytona Beach, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

Georgia Radiological Society
Secretary, Dr. B. H. Malone, 1406 Reynolds St., Brunswick, Ga.

Greater Miami Radiological Society
Secretary, Dr. George P. Daurelle, Jackson Memorial Hospital, Miami, Fla. Meets monthly third Wednesday at 8 P.M. at Mercy Hospital, Miami, Fla.

Greater St. Louis Radiological Society
Secretary, Dr. Thomas F. Maher, 1015 Missouri Theater Bldg., St. Louis, Mo.

Houston Radiological Society
Secretary, Dr. John M. Phillips, 1203 Ross Sterling Ave., Houston 25, Texas. Meets fourth Monday each month, Meeting Room, Doctors' Club of Houston.

Idaho State Radiological Society
Secretary, Dr. Alfred M. Stone, St. Lukes Hospital, Boise, Idaho. Meets annually at same time as Idaho State Medical Association.

*** Secretaries of societies are requested to send timely information promptly to the Editor.**

Illinois Radiological Society
Secretary, Dr. Stephen L. Casper, 1101 Maine St., Quincy, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. C. A. Stayton, 313 Hume-Mansur Bldg., Indianapolis 4, Ind. Meets first Sunday in May and during fall meeting of Indiana State Medical Association.

Iowa Radiological Society
Secretary, Dr. James T. McMillan, 1104 Bankers Trust Bldg., Des Moines, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. The scientific section is held in the autumn.

Kansas Radiological Society
Secretary, Dr. James R. Stark, 3244 E. Douglas, Wichita, Kansas. Meets in spring with State Medical Society, and in winter on call.

Kentucky Radiological Society
Secretary, Dr. Robert H. Akers, 1405 West Broadway, Louisville 3, Ky. Meets monthly on second Friday at Seelbach Hotel, Louisville.

Kings County Radiological Society
Secretary, Dr. Ernest I. Melton, 2187 Ocean Ave., Brooklyn 19, N.Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Putnam C. Kennedy, 540 N. Central Ave., Glendale 3, Calif. Meets second Wednesday of month in September, November, March, April and June at Los Angeles County Medical Association Building, Los Angeles.

Maine Radiological Society
Secretary, Dr. Francis J. O'Connor, Augusta General Hospital, Augusta, Maine. Meets in June, September, December and March.

Maryland Radiological Society
Secretary, Dr. Nathan B. Hyman, 1805 Eutaw Place, Baltimore, Md.

Memphis Roentgen Society
Secretary, Dr. James L. Booth, 899 Madison Ave., Memphis 3, Tenn. Meets first Monday of each month at John Gaston Hospital.

Miami Valley Radiological Society
Secretary, Dr. H. D. Robertson, Miami Valley Hospital, Dayton 9, Ohio. Meets second Friday of fall and winter months.

Mid-Hudson Radiological Society
Secretary, Dr. J. W. Walton, Horton Memorial Hospital, Middletown, N. Y. Meets 8:30 P.M., fourth Tuesday each month, September to May.

Milwaukee Roentgen Ray Society
Secretary, Dr. R. W. Bryne, 3321 N. Maryland Ave., Milwaukee 1, Wis. Meets monthly on fourth Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. O. J. Baggenstoss, 1953 Medical Arts Bldg., Minneapolis, Minn. Meets three times annually, once at time of State Med. Assn., and in spring and fall.

Mississippi Radiological Society
Secretary, Dr. Robert P. Henderson, 316 Medical Arts Bldg., Jackson, Miss. Meets third Thursday of each month at Hotel Edwards, Jackson, at 6:00 P.M.

Montana Radiological Society
Secretary, Dr. John Stewart, 1105 Frederick Lane, Billings, Montana. Meets at least once a year.

Nassau Radiological Society
Secretary, Dr. Jerome Zwanger, 126 Hicksville Rd., Massapequa, L. I., N. Y. Meets second Tuesday of the month in February, April, June, October and December.

Nebraska Radiological Society
Secretary, Dr. J. F. Kelly, Jr., 816 Medical Arts Bldg., Omaha, Neb. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. Raymond A. Dillon, 24 Wedgemere Ave., Winchester, Mass. Meets third Friday of each month, October through May, at Hotel Commander, Cambridge, Mass.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. Harold G. Jacobson, 210th St. and Bainbridge Ave., New York 67, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 4:30 P.M.

North Carolina Radiological Society
Secretary, Dr. William H. Sprunt, North Carolina Memorial Hospital, Chapel Hill, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. Marianne Wallis, St. Joseph's Hospital, Minot, N. D. Meetings by announcement.

North Florida Radiological Society
Secretary, Dr. Marvin Harlan Johnston, Five Points Medical Center, Jacksonville, Fla. Meets quarterly in March, June, September and December.

Northeastern New York Radiological Society
Secretary, Dr. Irving Van Woert, Jr., Albany Hospital, Albany, N. Y. Meets in Albany area on second Wednesdays of October, November, March and April.

Northern California Radiological Society
Secretary, Dr. H. B. Stewart, 2920 Capital Ave., Sacramento, Calif. Meets at dinner last Monday of each month, September to June.

Ohio State Radiological Society
Secretary, Dr. Francis C. Curtzwiler, 421 Michigan St., Toledo 2, Ohio. Annual meeting: May 16–18, 1958, Wade Park Manor Hotel, Cleveland, Ohio.

Oklahoma State Radiological Society
Secretary, Dr. Sol Wilner, St. John's Hospital, Tulsa, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. C. V. Allen, Veterans Hospital, Portland, Ore. Meets monthly from October to June on the second Wednesday of each month at 8:00 P.M. at the University Club.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets second Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. J. R. Raines, 214 Medical-Dental Bldg., Portland 5, Oregon. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. Walter P. Bitner, 234 State Street, Harrisburg, Pa. Annual meeting: Pittsburgh, Pa., May 16–17, 1958.

Philadelphia Roentgen Ray Society
Secretary, Dr. Roderick L. Tondreau, 3400 Spruce St., Philadelphia, Pa. Meets first Thursday of each month, at 5 P.M., from October to May in Thompson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. Edward M. Schultz, 3401 Fifth Ave., Pittsburgh, Pa. Meets second Wednesday of month, October through June at Hotel Roosevelt.

Radiological Section, Baltimore Medical Society
Secretary, D. James K. V. Willson, 1100 N. Charles St., Baltimore 1, Md. Meets third Tuesday each month, September to May, inclusive.

Radiological Section, Southern Medical Association
Secretary, Dr. Ted F. Leigh, Emory University, Georgia. Annual meeting: Miami Beach, Fla., November 11–14, 1957.

Radiological Society of Greater Cincinnati
Secretary, Dr. Warner Peck, Carew Tower St., Cincinnati 2, Ohio. Meets monthly from September to May on first Monday of each month at 7:30 P.M. at the Cincinnati General Hospital.

Radiological Society of Hawaii
Secretary, Dr. Jun-chu'an Wang, The Queen's Hospital,

Honolulu 9, Hawaii. Meets third Monday of each month alternately at 4:30 P.M. and 7:30 P.M.

Radiological Society of Greater Kansas City
Secretary, Dr. E. H. Stratemeier, Jr., 1010 Rialto Building, Kansas City 6, Mo. Meets last Friday of each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Radiological Society of Louisiana
Secretary, Dr. Seymour Ochsner, Ochsner Clinic, New Orleans 15, La. Meets annually during Louisiana State Medical Society Meeting.

Radiological Society of New Jersey
Secretary, Dr. Andrew P. Dedick, Jr., 67 E. Front St., Red Bank, N. J. Meets at Atlantic City at time of State Medical Society and in November in Newark, N. J.

Radiological Society of New York State
Secretary-Treasurer, Dr. Mario C. Gian, 610 Niagara St., Buffalo 1, N. Y. Meets with the State Medical Society in New York, May 11–16, 1958.

Radiological Society of Southern California
Secretary Dr. Harold P. Tompkins, 658 S. Westlake, Los Angeles, Calif.

Richmond County Radiological Society
Secretary, Dr. W. F. Hamilton, Jr., University Hospital, Augusta, Ga. Meets first Thursday of each month at various hospitals.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. John W. Colgan, 277 Alexander St., Rochester 18, N. Y. Meets at 8:15 P.M. on the last Monday of each month, September through May, at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. John H. Freed, 4200 East Ninth St., Denver 20, Colo. Annual meeting: To be announced.

St. Louis Society of Radiologists
Secretary, Dr. Edwin C. Ernst, Jr., 3720 Washington Ave., St. Louis 8, Mo. Meets fourth Wednesday each month, except June, July, Aug. and Sept.

San Antonio-Military Radiological Society
Secretary, Dr. Hugo F. Elmendorf, Jr., 730 Medical Arts Bldg., San Antonio 5, Texas. Meets Brooke Army Medical Center Officers Mess second Wednesday of each month.

San Diego Radiological Society
Secretary, Dr. J. C. Asher, 2001 Fourth Ave., San Diego 1, Calif. Meets first Wednesday of each month at the University Club.

San Francisco Radiological Society
Secretary, Dr. Irma Smith, 450 Sutter St., San Francisco 18, Calif. Meets quarterly at Grison's Steak House.

Section on Radiology, California Medical Association
Secretary, Dr. Nathan M. Spishakoff, 405 N. Bedford Dr., Beverly Hills, Calif.

Section on Radiology, Connecticut State Medical Society
Secretary, Dr. J. Burbank, Meriden Hospital, Meriden, Conn. Meetings are held bi-monthly.

Section on Radiology, Medical Society of the District of Columbia
Secretary, Dr. Charles E. Bickham, Jr., 1835 Eye St., N.W., Washington 6, D. C. Meets Medical Society Library, third Wednesday of January, March, May and October at 8:00 P.M.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. George E. Irwin, Jr., 703 N. East St., Bloomington, Ill.

Shreveport Radiological Club
Secretary, W. R. Harwell, 608 Travis St., Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M. September to May inclusive.

Society of Nuclear Medicine
Secretary, Dr. Robert Lackey, 452 Metropolitan Bldg., Denver 2, Colo. Annual meeting. June 19–21, 1958, Beverly Hilton Hotel, Los Angeles, Calif.

South Bay Radiological Society
Secretary, Dr. Howard L. Jones, Palo Alto Hospital, Palo Alto, Calif. Meets second Wednesday of each month.

South Carolina Radiological Society
Secretary, Dr. Wayne Reeser, 804 Burroughs St., Conway, S. C. One meeting with South Carolina Medical Association in May, others arranged by President.

Southern Radiological Conference
Secretary, Dr. Marshall Eskridge, Mobile Infirmary, Mobile, Ala.

Southwestern Radiological Society
Secretary, Dr. Gordon Black, Suite 2-A, El Paso Medical Center, 1501 Arizona, El Paso, Texas. Meets second Tuesday of each month.

Tennessee Radiological Society
Secretary, Dr. G. K. Henshall, 311 Medical Arts Bldg., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. J. E. Miller, Baylor Hospital, Dallas, Texas. Next meeting, January 24 and 25, 1958, San Antonio, Texas.

Tri-State Radiological Society
Secretary, Dr. Robert E. Beck, 600 Mary St., Evansville, Ind. Meets last Wednesday of Oct., Jan., March and May, 8:00 P.M. at Elks' Club in Evansville.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7:00 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May, Service Memorial Institute.

Upper Peninsula Radiological Society
Secretary, Dr. A. Gonty, Menominee, Mich. Meets quarterly.

Utah State Radiological Society
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets fourth Wednesday in January, March, May, September and November at Holy Cross Hospital.

Virginia Radiological Society
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Eva L. Gilbertson, 1317 Marion St., Seattle 4, Wash. Meets fourth Monday of each month from September through May at 610 Pine St., Seattle.

West Virginia Radiological Society
Secretary, Dr. W. Paul Elkin, 515 Medical Arts Bldg., Charleston, W. Va. Meets concurrently with annual meeting of West Virginia State Medical Society; other meetings arranged by program committee.

Westchester Radiological Society
Secretary, Dr. M. G. Priestman, New Rochelle Hospital, New Rochelle, N. Y. Meets on third Tuesday of January and October and on two other dates.

Wisconsin Radiological Society
Secretary, Dr. Farrell F. Golden, 5221 Tonyawatha Trail, Madison, Wis. Special meetings held during year; annual meeting each spring at Madison, Wis.

X-Ray Study Club of San Francisco
Secretary, Dr. John H. Heald, 450 Sutter St., San Francisco 8, Calif. Meets monthly, third Thursday at 7:30 P.M., Children's Hospital, September through June.

Cuba, Mexico, Puerto Rico and Central America

Sociedad de Radiología y Fisioterapía de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Sociedad Costarricense de Radiologia
Secretary, Dr. James Fernández Carballo, Apartado VIII, San Jose, Costa Rica.

Sociedad Mexicana de Radiología, A. C.
Calle del Oro No. 15, Mexico 7, D. F.
Secretary-General, Dr. Guillermo Santín. Meets first Monday of each month.

Asociación Puertorriqueña de Radiología
Secretary, Dr. R. B. Díaz Bonnet, Suite 504, Professional Bldg., Santurce, Puerto Rico.

Sociedad Radiológica Panameña
Secretary, Dr. L. Arrieta Sanchez, Apartado No. 86, Panama, R. de P. Meets monthly in a department of radiology of a local hospital, chosen at preceding meeting.

British Empire

Association of Radiologists of the Province of Quebec
Secretary, Dr. Isadore Sedlezky, 3755 Cote St. Catherine Rd., Montreal, Que. Meets four times a year.

British Institute of Radiology Incorporated with the Röntgen Society
Ordinary meeting, on the Thursday preceding the third Friday, October to May at 8:15 P.M.
Medical Members' meeting, on third Friday in each month at 5:00 P.M., 32 Welbeck St., London, W 1

Faculty of Radiologists
Honorary Secretary, Dr. R. A. Kemp Harper, 45, Lincoln's Inn Fields, London, W.C.2, England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Honorary Secretary, Dr. Guillaume Gill, *Associate Honorary Secretary*, Dr. Robert H. Fraser, 1555 Sommer Hill, Montreal, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Française d'Electro-Radiologie Médicales
General Secretary, Dr. Ls Ivan Vallée, 1058 rue St-Denis, Montreal 18, Canada. Meets third Saturday each month.

College of Radiologists (Australia and New Zealand)
Honorary Secretary, Dr. Alan R. Colwell, c/o British Medical Agency, 135 Macquarie St., Sydney, N.S.W.

South America

Asociacion Argentina de Radiologia
Secretary, Dr. Lidio G. Mosca, Avda. Gral. Paz 151 Córdoba, Argentina. Meetings held monthly.

Sociedad Argentina de Radiologia, Junta Central, Buenos Aires
Secretary, Dr. Juan L. Ambrogna, Montevideo 745, Buenos Aires. Meetings are held monthly.

Sociedad Argentina de Radiologia, Filial del Litoral, Sede, Rosario
President, Dr. Francisco P. Cifarelli. Meets monthly second Wednesday, 19 ha 663 Italia St., Rosario, Santa Fe.

Sociedad Argentina de Radiologia, Filial del Sur, Sede, La Plata
President, Prof. Dr. Jose P. Uslenghi, La Plata. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Centro Sede, Córdoba
President, Prof. Dr. David L. Caro, Corro 86, Córdoba. Meets monthly.

Sociedad Argentina de Radiologia, Filial del Norte, Sede, Tucuman
President, Dr. Julio Mendez Valladares, Rivadavia 358, Tucuman. Meets monthly.

Sociedad Argentina de Radiologia, Filial de Cuyo Sede, Mendoza
President, Dr. J. A. Orfila, Hospital Central, Mendoza. Meets monthly.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem. de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Oscar Rocha von Pfuhl, Av. Brigadeiro Luiz Antonio, 644 São Paulo, Brazil. Meets monthly on second Wednesday at 9:00 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Chilena de Radiologia
Secretary, Dr. Armando Doberti, Merced 565, Santiago, Chile. Meets fourth Friday of each month.

Sociedad Colombiana de Radiologia
Secretary, Dr. Luis E. Lozano B., Carrera 12 No. 20–69, 6° piso, Bogotá, Colombia. Meets last Thursday of each month.

Sociedad Ecuatoriana de Radiologia y Fisioterapia
Secretary, Dr. Enrique Ortega Guzmán, Casilla 4719, Guayaquil, Ecuador.

Sociedad Peruana de Radiologia
Secretary, Dr. Luis Pinillos G. Apartado 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta 218, Lima.

Sociedad de Radiologia del Atlantico
Secretary, Dr. Raul Fernandez, Calle 40 #41-110, Baranquilla, Colombia. Society meets monthly at the Instituto de Radiologia.

Sociedad de Radiología, Cancerología y Física Médica del Uruguay
Secretary-General, Dr. Roberto François, Av. Agraciada 1464, Piso 13, Montevideo, Uruguay.

Sociedade de Radiologia de Pernambuco
Secretary, Dr. Manoel Medeiros, Instituto de Radiologia da Faculdade de Medicina da Universidade do Recife, Caixa Postal 505, Pernambuco, Brazil.

Sociedad Venezolana de Radiología
Secretary, Dr. Otto Paz, Centro Médico, Caracas, Venezuela. Meets monthly third Friday at Colegio Médico del Distrito Federal, Caracas.

Continental Europe

Austrian Roentgen Society
President, Dr. Konrad Weiss, Mariannengasse 10, Vienna 9, Austria. Meets second Tuesday of each month in Allegemeine Poliklinik.

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 256 Chaussée de Wavre, Heverlee-lez-Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Société Française d'Electro-Radiologie Médicale, and its branches: Société du Sud-Ouest, du Littoral Méditerranéen, de Centre et du Lyonnais du Nord, de l'Ouest, de l'Est, et d'Alger et d'Afrique du Nord.
Secretary-General, Dr. Ch. Proux, 9, rue Daru, Paris 8e, France. Meets annually.

Ceskoslovensk společnost pro Rëntgenologii a Radiologii v Praze
Secretary, Dr. Roman Bláha, Praha XII, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Deutsche Röntgengesellschaft
Secretary, Dr. med. Peter Kröker, Evangelisches Krankenhaus, Huyssens Stiftung, (22a) Essen. Meets annually.

Società Italiana de Radiologia Medica e di Medicina Nucleare
Secretary, Dr. Ettore Conte, Ospedale Mauriziano, Torino, Italy. Meets annually.

Nederlandse Vereniging voor Electrologie en Röntgenologie
Secretary, Dr. J. R. von Ronnan, Violenweg 14, den Haag, Netherlands.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Española de Radiologia y Electrologia
Secretary, Dr. D. Aureo Gutierrez Churruca, Esparteros, No. 9, Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgen-Gesellschaft (Société Suisse de Radiologie)
Secretary, Dr. Max Hopf, Effingerstrasse 47, Bern, Switzerland.

India

Indian Radiological Association
Secretary, Dr. R. F. Sethna, Navsari Building, Hornby Road, Bombay 1, India.

The list of Meetings of Radiological Societies is published in every other issue of the Journal.

JAMES PICKER FOUNDATION AWARDS

On behalf of the James Picker Foundation, the National Academy of Sciences—National Research Council announces the continued availability of funds in support of radiological research. Applications are reviewed by the Committee on Radiology of the Academy—Research Council's Division of Medical Sciences. Final determination of awards is made by the Foundation upon recommendation of the Division.

In line with the interests of the Foundation, the program is oriented toward, but not necessarily limited to, the diagnostic aspects of radiology. Worthy applications in the field of veterinary radiology will be accepted and considered on their merits. Support is not restricted to citizens of the United States or to laboratories within this country.

Three specific types of support are offered:

(1) *Grants-in-aid* are designed to encourage investigations offering promise of improvement in radiological methods of diagnosis or treatment of disease. Research grants are awarded to institutions, rather than to individuals.

(2) *Grants for Scholars* are a transitional form of support, designed to bridge the gap between the completion of fellowship training and the period when the young scientist has thoroughly demonstrated his competence as an independent investigator. The application is submitted by the institution on behalf of the prospective Scholar. If the request is approved, a grant of $6,000 per year will be made directly to the institution as a contribution toward the Scholar's support, or his research, or both. Initial grants are limited to one year, but renewal for two additional years may be recommended.

(3) *Fellowships in Radiological Research* are open to candidates seeking to gain research skills leading to investigative careers in the field of radiology. While persons from closely related disciplines are eligible to apply, candidates whose training has been directly in the field of radiology will receive preference under this program. Candidates must hold the M.D., Ph.D., or Sc.D. degree or the equivalent. Preference will be given to applicants who are thirty-five years of age or less.

Applications in these three categories for the fiscal year 1958–1959 should be submitted by December 1, 1957. Further details and application blanks may be obtained from the *Division of Medical Sciences—Room 309, National Academy of Sciences—National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.*

The National Research Council of Canada will in the near future assume the responsibility for serving as scientific adviser to the James Picker Foundation with respect to its Canadian program.

DR. JOHN CAFFEY HONORED

Dr. John Caffey, professor of Radiology, College of Physicians and Surgeons, Columbia University, was elected an Honorary Member of the Royal Society of Medicine, at its London meeting on May 7, 1957, "in recognition of his distinguished services to science." Dr. Caffey was also elected an Honorary Member of the American Orthopedic Association at its June meeting.

ORINS OFFERS RADIOISOTOPES COURSES

The Special Training Division of the Oak Ridge Institute of Nuclear Studies has announced the following 1958 schedule of four-week courses in the basic techniques of using radioisotopes: January 6–31, February 3–28, May 19–June 13, June 16–July 11, August 11–September 5, September 8–October 3. Minimum scholastic requirement for admission to the courses is a bachelor's degree, preferably in a scientific field. Further information concerning these courses may be obtained by writing Dr. Ralph T. Overman, Chairman, Special Training Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tennessee.

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interest of our readers as space permits.

Dermatology. By Donald M. Pillsbury, M.A., D.Sc.(Hon.), M.D., Professor and Director of Department of Dermatology, University of Pennsylvania School of Medicine; Walter B. Shelley, M.D., Ph.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine; and Albert M. Kligman, M.D., Ph.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine. Cloth. Price, $20.00. Pp. 1,331, with 564 figures. W. B. Saunders Company, 218 West Washington Square, Philadelphia 5, Pennsylvania, 1956.

This outstanding volume attempts the long awaited organization of dermatology into modern scientific concepts. The authors are the impressive dermatologic research team of the University of Pennsylvania, and are singularly equipped for their task. It is fitting that they should dedicate this book to their progenitors, Drs. John Stokes and Fred Weidman, giants of the era past.

Departing radically from the standard dermatologic text form, the first thirteen chapters deal succinctly and definitively with application of basic fundamental principles necessary for an understanding of the structure and function of the skin. Besides their masterful presentation there is a concise italized summary at the end of each chapter useful for quick review.

The remainder of the book deals with "Basic Principles and Clinical Application of Allergy and Hypersensitivity," "Principles of Diagnosis," "Dermatologic Therapy," and "Cutaneous Medicine."

The etiologic emphasis is that of Stokes, namely the very necessary understanding of "multiple causal factors" in the genesis of disease of the skin. Exemplifying this arrangement are graphic cartoons depicting the burdened patient bearing his cross of causal factors—trauma, infection, allergy, vasomotor state, psyche, civilization, atopy, constitutional factors, etc.

The chapter on "Dermatologic Therapy" is simple and useful. It has been reprinted by the Veterans Administration in the form of a technical bulletin used by their professional staff. Since the orientation of the book is physiologic, treatment becomes rational and well organized. The formulary used consists of tested and simple remedies which are effective and not too expensive or complex. A novice utilizing their approach and formulary can probably successfully treat the great bulk of dermatologic situations that he will encounter.

The one disquieting feature of this book to this reviewer is the cynical attitude toward the use of ionizing radiation in dermatologic therapy. The excellent work of the group, especially Dr. Pillsbury, on the use of Grenz ray in dermatology partially accounts for this, since he feels quite strongly that this modality is much safer, especially in the hands of the average practitioner. Superficial radiation therapy has stood the test of time in the dermatologist's armamentarium. Despite the inadequate safety features, precarious equipment, crude quantitation of radiation output accompanying the early years of this mode of therapy, dire sequelae are in the great minority and should decrease further with the use of modern equipment properly calibrated, improved training in basic fundamentals (physics, etc.), understanding of dosage maximums and true indications for use. It would seem that our concern regarding radiation, whether diagnostic or therapeutic, should lessen rather than increase, but unfortunately this is complicated by an atom aware, radiation conscious, frightened public fed by an intemperate lay press (as well as supported from certain medical sources). Yet these data are far from conclusive and the final castigation of therapeutic radiation awaits much more study. The safe use of irradiation, like that of any other therapy, depends in part on the human factor, *i.e.* the judgement, knowledge, and conscience of the practitioner.

The book includes a chapter on surgical diathermy and ultraviolet light. The infectious diseases are superbly covered and one is surprised and pleased by such bits of information as: impetigo is not contagious, and indeed is difficult to transmit in the adult. Other excellent chapters include: dermatologic parasitology

(in readable form); nevus tumors, their clinical differentiation and their management; a comprehensible discussion on nail anatomy, physiology and disease; expert discussion of the structure, function and pathology of the skin appendages (hair, apocrine, eccrine, sebaceous glands, etc.); an unusual and needed discussion on hereditary dermatology and a chapter on psychocutaneous disease, an ever enlarging subject written by a psychoanalyst with practical dermatologic experience, Philip Seitz.

This book should revolutionize the teaching of modern dermatology. It provides a readable, scientific, comprehensive and logical text from which any student or physician can glean the theory, practice, and eventual objectives of this specialty now in its renaissance. It should be on every medical bookshelf.

Arthur C. Curtis, M.D.

Rare Earths in Biochemical and Medical Research: A Conference Sponsored by the Medical Division, Oak Ridge Institute of Nuclear Studies, October 1955 (United States Atomic Energy Commission). Edited by Granvil C. Kyker and Elizabeth B. Anderson. Paper. Price, $2.20. Pp. 468, with numerous figures and tables. Available from the Office of Technical Services, Department of Commerce, Washington 25, D. C., 1956.

Although the rare earths have been the subject of considerable study for some 160 years since the isolation of yttria in 1794, it was the occurrence of these elements in fission products which first attracted intensive biochemical and medical interest. This has particularly stimulated investigation of the radioactive rare earth isotopes from two contrasting aspects: as potential health hazards and as controlled sources of radiation for therapeutic purposes.

This report of a conference in October 1955, sponsored by the Medical Division of Oak Ridge Institute of Nuclear Studies and initially inspired by the late Dr. Kurt G. Stern of the Montefiore Hospital group, who were among the earliest and most active workers in this field, includes 33 papers on the chemical and pharmacologic aspects of the rare earth elements, the production of isotopes of special interest, with the spatial emphasis (301 out of 443 pages) on the biologic and metabolic characteristics, clinical applications and dosimetry. The formal papers are followed by verbatim reports of the impromptu discussions; where the comment "don't put that in" occurs, the instruction is, happily, ignored.

The inclusion of a comprehensive index, so often omitted from reports of this type, together with references to sources of supply adds greatly to the usefulness of this publication. The diagrams are, in general, models of clarity and the graphs are reproduced on an admirably large scale, frequently full-page, but in many cases the addition of the principal coordinate squares would have been an advantage. Also, many readers, less familiar than the conference members with the rare earth isotopes, will regret the absence of a table of their radioactive characteristics, although this information is given for accelerator produced isotopes. It must, of course, be remembered that in spite of the commendable alacrity with which these reports are produced, there is still an interval of a year between the time of the conference and the publication date; long enough for considerable progress in so rapidly advancing a field.

The true rare earths, or lanthanons, include elements 57–71 to which scandium (21) and yttrium (39) are added because of many chemical resemblances; there are also many similarities to the heavier actinide group. In this report attention is focussed on the lanthanons and yttrium because of the primary interest in beta and gamma emitters. Although these elements are, in fact, by no means rare in nature, concentrated deposits are not common and the chemistry involves many difficult problems of separation. Surveys are included of both reactor and cyclotron produced isotopes, the latter being a very valuable source of high specific activity and carrier free material.

The papers dealing with the distribution, toxicity and metabolism are of principal medical interest while radiologists will probably turn first to the applications and dosimetry. Reports on animal experiments are followed by preliminary clinical studies with yttrium 90 and lutecium 177. It is found that, following intravenous injection, the plasma concentration decreases much more slowly with Y^{90} than for Au^{198} but after intracavitary (peritoneal or pleural) injection the concentration and urinary excretion follow a similar pattern in both cases. Lu^{177} behaves analogously and for both, a high carrier concentration leads to a markedly increased removal rate from the cavity fluid. While Y^{90} is localized in the skeleton, the distribution differs from that of Ca and Sr and the association is with highly calcified bone surfaces

and not with the uncalcified osteoid matrix as previously reported. The use and dosimetry of small beta-ray sources, Y^{90} impregnated gelfoam and solutions of gamma-ray emitters in polyethylene tubing to form linear sources are described.

The report concludes with a characteristically Brucerian summing-up of the proceedings.

RAYMOND S. QUICK

PROGRESS IN RADIOBIOLOGY. Proceedings of the Fourth International Conference on Radiobiology held in Cambridge on 14th to 17th August, 1955. Edited by Joseph S. Mitchell, Barbara E. Holmes, and Cyril L. Smith, Department of Radiotherapeutics, University of Cambridge. Cloth. Price, $12.75. Pp. 557, with numerous illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1956.

These carefully edited papers are presented in book form. They are divided in various sections: genetics, oxygen effects, relative biologic efficiency, effects of radiations on the metabolism of enzymes, carcinogenesis, etc. References are listed for each presentation which is followed by a transcript of the discussions. The result is a valuable volume, filled with the most interesting information on the different aspects of research in the field of radiobiology.

One cannot but echo the editors' hope that radiobiologic research may open new avenues in the application of radiations to the treatment of cancer. But the endeavors here presented are playing to a larger audience, for radiobiologic research has acquired importance of much greater proportions in human society.

J. A. DEL REGATO, M.D.

LYMPHATICS, LYMPH AND LYMPHOID TISSUE. By Joseph Mendel Yoffey, D.Sc., M.D. (Manch.), F.R.C.S.(Eng.), Professor of Anatomy, University of Bristol; and Frederick Colin Courtice, M.A., D.Phil.(Oxon.), D.Sc. (Sydney), F.R.A.C.S.(Hon.), Director, Kanematsu Memorial Institute of Pathology, Sydney Hospital, Sydney. Cloth. Price, $10.00. Pp. 510, with 99 illustrations and 55 tables. Published for The Commonwealth Fund by the Harvard University Press, 44 Francis Avenue, Cambridge 38, Massachusetts, 1956.

This is a complete revision of the book of the same title under authorship of C. K. Drinker and J. M. Yoffe, published in 1941.

The book has been extensively rewritten and reindexed with the addition of many new figures. The bibliography is distributed at the end of each chapter, has been brought up to date and has retained the necessary background of classic articles. Information is readily available on any phase of the anatomy, histology and physiology of the lymphatic system.

Of interest to radiologists will be the discussion of the response of lymphatic tissues to radiation. The presentation of the latest research on the relation of stress, the alarm reaction, and steroid hormones to the lymphatic system will interest clinicians as well as physiologists and pathologists. The role of lymph and permeability to the maintenance of fluid balance and the mechanisms and functions of the lymphatic system in inflammation are of general interest.

The book is not only valuable for reference but is so well written that it can be read without fatigue.

W. L. BROSIUS, M.D.

BLADDER TUMORS: A Symposium. Under the auspices of The American Cancer Society. Cloth. Price, $4.00. Pp. 92, with numerous illustrations. J. B. Lippincott Company, East Washington Square, Philadelphia 5, Pennsylvania, 1956.

This symposium, first published in *Cancer* (May and June 1956), is now made available in a book form. It deals with the current endoscopic and surgical methods used for treatment of bladder tumors. The methods and effects of radiation therapy are excluded. This perhaps enhances the value of the book, since with our present multiplicity of ways and combination of ways, the proper treatment of bladder tumor has reached a confused state.

Many authors have contributed to the various articles, but Victor A. Marshall appears most often as the common author.

The first article entitled "Current Clinical Problems Regarding Bladder Tumors," poses the questions which the subsequent articles, mainly by tedious and detailed statistical analyses, attempt to answer. The dual pathologic classification by grade, as originated by Broder, and more recently by stage, as outlined by Jewett and Strong, acts as the basis for comparison in the various forms of treatment to follow.

The second article deals with a series of cases of bladder tumor, for which no treatment was

given, outlining the clinical course, morbidity, and survival time.

The following seven articles attempt to show statistically the effect of treatment on the survival time, as compared to the untreated group, and against one another. The methods of therapy discussed are: (1) fulguration and excision, (2) segmental resection, (3) simple cystectomy, and (4) radical segmental or total cystectomy.

An article follows summarizing the findings and establishing an organized program for treatment of bladder tumors, using the above mentioned procedures.

Three interesting articles are included entitled, "Pelvic Exenteration for Polypoid Myosarcoma of the Urinary Bladder of an Infant"; "Hormonal Influences on the Experimental Production of Bladder Tumors in Dogs"; and "Secondary Carcinoma of the Penis."

The forms of therapy discussed in the symposium are of great interest to the urologist, and of general interest to the radiologist. Considerable time, thought, and effort has gone into the collection of the material for drawing the many important conclusions based upon years of experience and statistical facts.

Robert C. Thumann, M.D.

Stratiterapia Bifocale. By G. Tori, G. Brusori, R. Miceli, and E. Zaffagnini. Cloth. Pp. 146, with 59 illustrations. Casa Editrice L. Cappelli, Bologna, Italy, 1956.

The authors report on the use of a new therapeutic equipment designed by Professor G. G. Palmieri. This equipment consists of two tubes placed one above and one below the patient. These two tubes are connected to the treatment couch by rods in a fashion similar to that used in linear laminagraphy. The couch itself is moved by motors in longitudinal or transverse directions, and the two motions may be combined and varied in extent.

This equipment makes it possible to modify the dosage distributions in depth with remarkable flexibility. The authors believe that the method is much superior to the usual rotational or pendular therapy whenever one desires a uniform dosage over a large volume of tissue.

This is a very interesting approach to therapeutic problems. Numerous isodose charts of various areas of the body with various combinations of motions are included. This book is concerned only with the physical aspects of the system. The clinical results are being collected and will form the subject of a later report.

Cesare Gianturco, M.D.

Souvenir Number of The Indian Journal of Radiology, 1956; In Commemoration of the Diamond Jubilee of the Discovery of X-Rays by Professor Dr. Wilhelm Conrad Röntgen. K. P. Mody, Editor-in-Chief. Paper. Pp. 702, with numerous illustrations. Indian Journal of Radiology, Navsari Building, Dr. Dadashoy, Naoroji Road, Fort, Bombay 1, India, 1956.

This volume of 702 pages, celebrating the diamond jubilee (60 years) of Roentgen's discovery (November 8, 1895), is dated 1956, and was distributed in 1957. It contains 22 papers on diagnostic roentgenology, 4 on the history, teaching, and organization of radiology, 19 on radiation therapy, and 16 on physics and biology. Only the preface, the foreword, and one editorial are contributed by Indian authors. A total of 22 papers originated in the British Isles, 20 came from the U.S.A., 5 each from the U.S.S.R. and Germany, 2 each from Canada and the Netherlands, and 1 each from France, Denmark, Israel, South Africa, and Sweden.

As expected, there is a wide variation in the quality of the contributions. Special mention should be made of the following articles: The practical review of methods for the visualization of the biliary tract by Wm. H. Shehadi (U.S.A.); the use of body section roentgenography for the study of pulmonary vascularization by Th. Hornykiewitsch (Germany); the identification of the crico-pharyngeus muscle on esophagograms by T. V. L. Chrichlow (England); an historical article on radiological education in the United Kingdom by G. Stead (England); reviews on the therapeutic use of radioactive isotopes, by W. S. Scott (U.S.A.), and J. S. Mitchell (England); a progress report on the progeny of previously sterile females, treated with roentgen therapy, including photographs of almost 50 prosperous looking children and grand-children by Ira I. Kaplan (U.S.A.); a monographic paper on roentgen- and telecurietherapy of laryngeal carcinoma by M. Lederman (England); description of a newly developed shadow microscope with a sectional electronic roentgen tube, acting as a microprojector, which results in a resolving power of less than one micron, by B. M. Rovinsky, V. G. Lutsau, and A. I. Avdeenko (U.S.S.R.), and a progress review of the employment of

radioactive isotopes for the roentgenography of the human body by W. V. Mayneord and H. J. D. Ireland (England).

Of interest to radiologists in the Western Hemisphere are the five articles by Russian authors. Aside from the above mentioned, strictly scientific and most certainly valuable, contribution on roentgen microscopy, there is a brief review of Soviet roentgen engineering written by an expert. This review includes some original information as, for instance, the observation that the life of oil-cooled tubes is greatly increased if they are placed horizontally, and not with the anode downwards, because in the latter case the circulation of the cooling oil stops in the anode neck with consequent overheating of the inner parts (it is another question how feasible this horizontal position is from a technical viewpoint, and also for the anode heel phenomenon). By contrast, the exposé of trends and organization of radiology in the U.S.S.R., by I. G. Lagunova, attempts to prove that its development in Russia was possible only because of direct governmental support. Less obvious in its political motivation is the mildly philosophical paper by Y. N. Sokolov, who believes that the peculiarity of Soviet roentgenology is its "clinical trend," i.e. the fact that the roentgen examination is only part and parcel of the general examination of the patient; in his well-balanced survey of present day Russian roentgenologic literature (in which he quotes also the German phthisiologist Ranke, the French broncholologists Sicard and Forestier, and the American bronchoscopist Chevalier Jackson and radiologist Pancoast), he shows that their subjects of endeavor are very similar to those in the Western publications. Conversely, in the highly nationalistic article by L. D. Podlyashuk on the main trends of radiobiology and radiotherapy in the U.S.S.R. emphasis is placed on the radiation therapy of nonmalignant diseases, from tonsillitis, pulmonary abscess, and C.N.S. syphilis, to scleroma, leishmaniosis, and wartime peptic ulcer.

In summing up, one may conclude that, despite the inevitable heterogeneity of the material included, every radiologist will find in this souvenir number something of interest. Even if he should happen to disagree with some (or with many) of the statements printed, it will at least give him food for thought, which in itself is a significant accomplishment to be credited to the Indian editors.

E. R. N. Grigg, M.D.

BOOKS RECEIVED

Twenty-second Semiannual Report of the Atomic Energy Commission. By United States Atomic Energy Commission. Paper. Pp. 257, with illustrations and tables. United States Government Printing Office, Washington, D. C., 1957.

The Proximal End of the Femur; Investigations with Special Reference to the Etiology of Femoral Neck Fractures. Acta radiologica, Supplement 146. By Stig Backman. Paper. Price, Sw. Kr. 35:–. Pp. 166, with 70 illustrations. Acta radiologica, Stockholm 2, Sweden, 1957.

Changes in Liver Cell Elements During Stimulated Protein Synthesis; A Cytochemical Study. Acta radiologica, Supplement 147. By G. F. Bahr. Paper. Price, Sw. Kr. 25:–. Pp. 111, with 59 illustrations. Acta radiologica, Stockholm 2, Sweden, 1957.

Demographic Studies on Carcinoma of the Uterine Cervix in Sweden; Part I. Acta radiologica, Supplement 145. By O. G. A. Berggren. Paper. Price, Sw. Kr. 30:–. Pp. 147, with diagrams and tables. Acta radiologica, Stockholm 2, Sweden, 1957.

Selektive Lungenangiographie in der präoperativen Diagnostik und in der inneren Klinik. By Prof. Dr. W. Bolt, Köln, Prof. Dr. W. Forssmann, Bad Kreuznach, and Landesmed.-Dir. Dr. H. Rink, Marienheide. Cloth. Price, DM 54.—. Pp. 200, with 205 illustrations. Georg Thieme, Herdweg 63, Stuttgart, Germany, 1957.

Gastro-Intestinal Obstruction. By Meyer O. Cantor, M.D., M.S., F.A.C.S., Associate Attending Surgeon, Grace Hospital; Attending Surgeon, Sinai Hospital of Detroit; Former Attending Surgeon, Deaconess Hospital; and Roland P. Reynolds, M.D., F.A.C.S., Chief of Surgery, Grace Hospital. Cloth. Price, $18.00. Pp. 565, with 415 illustrations. The William & Wilkins Company, Mount Royal and Guilford Avenues, Baltimore 2, Maryland, 1957.

Degenerative Changes in the Sternoclavicular and Acromioclavicular Joints in Various Decades. By Anthony F. DePalma, M.D., James Edward Professor and Head of the Department of Orthopaedic Surgery, Jefferson Medical College. Cloth. Pp. 178, with 105 illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1957.

The Salient Points and the Value of Venous Angiocardiography in the Diagnosis of the Cyanotic Types of Congenital Malformations of the Heart. By Benjamin M. Gasul, M.D., Gershon Hait, M.D., Robert F. Dillon,

M.D., and Egbert H. Fell, M.D. Cloth. Price, $3.50. Pp. 80, with illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1957.

Bronchiectasis; Radiological Diagnosis and Prognosis After Operative Treatment. Acta radiologica, Supplement 143. By Carl Einer Gudbjerg. Paper. Price, Sw. Kr. 25:–. Pp. 115, with 45 illustrations. Acta radiologica, Stockholm 2, Sweden, 1957.

Movement of the Heart and Blood in Animals; An Anatomical Essay by William Harvey. Translated from the original Latin by Kenneth J. Franklin, and now published for the Royal College of Physicians of London. Cloth. Price, $3.50. Pp. 209. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1957.

Intermediate Reactions in the Coagulation of Blood with Tissue Thromboplastin. The Scandinavian Journal of Clinical & Laboratory Investigation, Volume 9, Supplement 27. By Peter F. Hjort. Paper. Pp. 183, with 64 illustrations. The Scandinavian Journal of Clinical & Laboratory Investigation, Department A, Rikshospitalet, Oslo, Norway, 1957.

Isotopic Tracers in Biology; An Introduction to Tracer Methodology. By Martin D. Kamen, Associate Professor of Radiochemistry, Edward Mallinckrodt Institute of Radiology, Washington University Medical School, St. Louis, Missouri. Third edition. Cloth. Price, $9.50. Pp. 474, with 70 illustrations. Academic Press Inc., Publishers, 111 Fifth Avenue, New York 3, New York, 1957.

Progress in Gynecology. Volume III. Edited by Joe V. Meigs, M.D., Clinical Professor of Gynecology, Harvard Medical School; and Somers H. Sturgis, M.D., Clinical Professor of Gynecology, Harvard Medical School. Cloth. Price, $15.50. Pp. 780, with numerous illustrations. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, New York, 1957.

Current Surgical Management; A Book of Alternative Viewpoints on Controversial Surgical Problems. Edited by John H. Mulholland, M.D., New York University College of Medicine; Edwin H. Ellison, M.D., Ohio State University College of Medicine; and Stanley R. Friesen, M.D., University of Kansas Medical Center; with contributions by 76 American Authorities. Cloth. Price, $10.00. Pp. 494, with illustrations. W. B. Saunders Company, 218 West Washington Square, Philadelphia 5, Pennsylvania, 1957.

Testing and Teaching of Photofluorogram Interpreters. By Helge Nielsen, Department for Mass Radiography, Central Chest Clinic, Copenhagen. Paper. Pp. 33, with illustrations. Ejnar Munksgaards, Nørregade 6, Copenhagen, Denmark, 1957.

Science Looks at Smoking. By Eric Northrup. Cloth. Price, $3.00. Pp. 190. Coward McCann, Inc., 2 West 45th Street, New York 19, New York, 1957.

Symposium on Biocolloids. Sponsored by The Biology Division, Oak Ridge National Laboratory. Paper. Free of charge to scientific investigators. Pp. 322, with numerous figures and tables. Oak Ridge National Laboratory, Post Office Box Y, Oak Ridge, Tennessee, 1957.

Maladies des Veines; Diagnostic et Traitement. By Claude Olivier, Agrégé de la Faculté de Médecine de Paris, Chirurgien des Hôpitaux. Cloth. Price, 7,400 fr. Pp. 600, with 243 illustrations. Masson et C^ie^, Éditeurs, 120 boulevard Saint-Germain, Paris 6^e^, France, 1957.

Quantitative Roentgenologic Studies on Changes in Mineral Content of Bone in Vivo. Acta radiologica, Supplement 148. By Karl-Åke Omnell. Paper. Price, Sw. Kr. 25:–. Pp. 86, with illustrations. Acta radiologica, Stockholm 2 Sweden, 1957.

Radiologie Clinique de l'Estomac Opéré. By P. Porcher, Médecin Radiologiste de l'Hôpital Saint-Antoine et de l'Hôpital Américain, Membre de l'Académie de Chirurgie; and P. Buffard, Médecin Radiologiste des Hôpitaux de Lyon. Cloth. Price, 8,000 fr. Pp. 660, with 507 illustrations. Masson et C^ie^, Éditeurs, 120 boulevard Saint-Germain, Paris 6^e^, France, 1957.

Berättelse från Styrelsen för Cancerföreningen I Stockholm över Verksamhetsåret 1956; Redogörelser för Verksamheten å Radiumhemmet, Radiopatologiska Institutionen Och Radiofysiska Institutionen Vid Konung Gustaf V:S Jubileumsklinik I Stockholm under År 1956; Index of Papers Published at the Radiumhemmet, the Institute of Radiopathology and the Institute of Radiophysics; Report of Dec. 31st, 1956, on Patients Registered at the Radiumhemmet 1921–1956. Paper. Pp. 152, with tables. K. K. Beckmans Boktryckeri, Stockholm, Sweden, 1957.

Pneumoencephalography. By E. Graeme Robertson, M.D. (Melb.), F.R.C.P., F.R.A.C.P., Honorary Neurologist, Royal Melbourne Hospital and Royal Children's Hospital. Cloth. Price, $14.50. Pp. 482, with 209 illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1957.

Il Pneumoretroperitoneo. By L. Rossi and A. Baronchelli. Paper. Pp. 217, with 210 illustrations. Cappelli, Via Farini, 6, Bologna, Italy, 1957.

Selected Papers from the Institute of Cancer Research: Royal Cancer Hospital and from the Royal Marsden Hospital 1955. Published by order of the Committee of Management of the Institute and the Board of Governors of the Royal Marsden Hospital, London. Volume 10.

Cloth. Pp. 808, with numerous illustrations. Chester Beatty Research Institute, Fulham Road, London, S.W.3, England, 1957.

Fortschritte der Kiefer- und Gesichts-Chirurgie; Ein Jahrbuch. Volume III. By Prof. Dr. K. Schuchardt, Direktor der Klinik und Poliklinik für Zahn-, Mund- und Kieferkrankheiten der Universität Hamburg und der Nordwestdeutschen Kieferklinik. Cloth. Price, DM 96.—. Pp. 359, with 391 illustrations. Georg Thieme, Herdweg 63, Stuttgart, Germany, 1957.

The Hemodynamics of the Lesser Circulation in Pulmonary Tuberculosis. The Scandinavian Journal of Clinical & Laboratory Investigation, Volume 9, Supplement 26. By Bror Söderholm. Paper. Pp. 111, with 13 figures. The Scandinavian Journal of Clinical & Laboratory Investigation, Department A, Rikshospitalet, Oslo, Norway, 1957.

Influence of Posture on the Lung Volumes, Ventilation and Circulation in Normals; A Spirometric-Bronchospirometric Investigation. The Scandinavian Journal of Clinical & Laboratory Investigation, Volume 9, Supplement 25. By Lawe Svanberg. Paper. Pp. 195, with figures and tables. The Scandinavian Journal of Clinical & Laboratory Investigation, Department A, Rikshospitalet, Oslo, Nowray, 1957.

Rotation Radiography. By Shinji Takahashi, M.D., Professor of Radiology, School of Medicine, University of Nagoya, Head of the Department of Radiology, Hospital of the University of Nagoya, in Japan; and Professor of Radiology, School of Medicine, University of Hirosaki, Head of the Department of Radiology, Hospital of the University of Hirosaki, in Japan. Cloth. Pp. 184, with 118 illustrations. Published by the Japan Society for the Promotion of Science, 1957. (Sales agent: Maruzen Co. Ltd., Nihonbashi, Tokyo, Japan.)

Experimental Studies on the Disappearance of Radiosodium Ions with Local Deposits in the Cavity and in the Wall of the Vagina of the Rat. Acta radiologica, Supplement 144. By Björn Westin. Paper. Price, Sw. Kr. 30:–. Pp. 87, with 41 illustrations. Acta radiologica, Stockholm 2, Sweden, 1957.

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The Year Book of Cancer, 1956–1957. Compiled and edited by Randolph Lee Clark, Jr. B.S., M.D., M.Sc. (Surgery), D.Sc. (Hon.), Director and Surgeon-in-Chief, The University of Texas M. D. Anderson Hospital and Tumor Institute; Professor of Surgery, The University of Texas Postgraduate School of Medicine; Clinical Professor of Surgery, Baylor University College of Medicine; and Russell W. Cumley, B.A., M.A., Ph.D., Director of Publications, the University of Texas M. D. Anderson Hospital and Tumor Institute; Professor of Medical Journalism, The University of Texas Postgraduate School of Medicine. Cloth. Price, $7.50. Pp. 572, with 209 illustrations. Year Book Publishers, Inc., 200 E. Illinois Street, Chicago 11, Illinois, 1957.

Medical Radiation Biology. By Friderich Ellinger, M.D., Chief Radiation Biologist and Head, Pharmacology Division, Naval Medical Research Institute; Member, Radioisotope Board and Consultant to the Tumor Board, U. S. Naval Hospital, Bethesda, Maryland. Cloth. Price, $20.00. Pp. 945, with numerous illustrations. Charles C Thomas, Publisher, 301 East Lawrence Avenue, Springfield, Illinois, 1957.

Die heutige Behandlung der Skelett-Tuberkulose des Kindes und des Jugendlichen. By Dr. G. Glogowski, Wissenschaftlicher Oberassistent an der Orthopädischen Klinik München. Paper. Price, DM 10.80. Pp. 61, with 54 illustrations. Georg Thieme, Herdweg 63, Stuttgart, Germany, 1957.

Die vaskulären Erkrankungen im Gebiet der Arteria Vertebralis und Arteria basalis; Eine anatomische und pathologische, klinische und neuroradiologische Studie. By Prof. Dr. H. Krayenbühl, Direktor der Neurochirurgischen Universitätsklinik Zurich; and Dr. G. Taşargil, Assistent der Neurochirurgischen Universitätsklinik Zurich. Cloth. Price, DM 77.—. Pp. 170, with 25 illustrations. Georg Thieme, Herdweg 63, Stuttgart, Germany, 1957.

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ABSTRACTS OF RADIOLOGICAL LITERATURE

Department Editor: T. Leucutia, M.D., Harper Hospital, Detroit 1, Michigan

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ROENTGEN DIAGNOSIS

Neck and Chest

Villar, Thome George. O interesse da broncografia no estudo dos tumores broncopulmonares. (The importance of bronchography in the study of broncho-pulmonary tumors.) *Acta iber. radiol. cancerol.*, Oct.–Dec., 1956, *11*, 425–438. (From Serviço de Patologia Médica da Faculdade de Medicina, Lisbon, Portugal.)

This paper reports the experiences gained during the performance of bronchograms in 36 patients (from a total of 200) which had broncho-pulmonary tumors. There were 3 with benign tumors (angiomatoid adenoma of the trachea; hemangioma of the right main bronchus; adenoma of the right main bronchus), which presented the classic narrowing of the bronchial lumen, with a distal dilatation, thus forming a small "gutter" of bronchographic medium around the growth.

Conversely, malignant tumors, by their very invasiveness, are not likely to be well delimitated, and the often encountered infiltration of the bronchial walls will cause a rigidity of the bronchi, which can be detected during fluoroscopy by the localized absence of bronchial motility in the course of respiratory movements. Intrabronchial malignancies cause obstructive phenomena, usually well demonstrated on bronchography, being either partial (filiform or infundibuliform), or total (conical or amputated). One must be cautious in interpreting complete obstruction, because technical artefacts should first be ruled out.

While bronchoscopy is often of help in the above described eventualities, its usefulness is very limited or nil in extrabronchial tumors. Yet even in the latter cases, bronchography may provide a diagnostic appearance, by showing extrinsic pressure upon adjacent bronchi, which are so displaced as if they were draped around the tumor.

Several illustrative cases are included, and support the concept that correlation of the bronchographic results with the bronchoscopic findings, with biopsy, and with the other clinical and laboratory examinations will enhance the chances for a correct preoperative diagnostic impression.—*E. R. N. Grigg, M.D.*

Ferguson, Charles F., and Flake, Carlyle G. Bronchography in the diagnosis of pediatric problems. *J.A.M.A.*, June 1, 1957, *164*, 518–521. (Address: C. F. Ferguson, 300 Longwood Avenue, Boston, Mass.)

Advances in pediatric, thoracic and cardiovascular surgery have made remedy of many broncho-pulmonary abnormalities possible. For maximum benefit, early diagnosis is essential, and for the accomplishment of early diagnosis bronchography is a very important part of the investigation.

The clinical symptoms which should alert the physician to the probable need for a thorough chest examination are:

1. Chronic pulmonary changes demonstrable by the usual roentgenographic study.
2. Unexplained chronic cough, whether productive or nonproductive.
3. Stridor.
4. Recurring infection in the same area of the lung.
5. Persistent recurrent wheezing emanating from the same area of the lung.
6. Hemoptysis.

Although bronchiectasis is today frequently treated successfully by medical therapy alone, an accurate evaluation of the condition of the tracheobronchial tree should be carried out before such treatment is undertaken. Such etiologic factors as congenital anomaly of a bronchus with or without stenosis, weakness, malformation or absence of cartilaginous ring in the main bronchi, and foreign body obstruction of a bronchus must be recognized before successful treatment can be accomplished.

The diagnosis of agenesis of the lung, whether it be a true aplasia, a tiny out-pocketing of the trachea, or extreme hypoplasia of a bronchus can be established by bronchography.

Tracheoesophageal fistula, particularly if the esophagus is patent, may give no symptoms except recurrent attacks of pneumonitis of the aspiration type. Such fistula may be overlooked until late in infancy or childhood. Bronchography may be of great help in delineating the fistula if it has not already been demonstrated fluoroscopically by means of barium studies of esophagus. Early diagnosis permits surgical repair before the development of chronic pneumonitis with resultant fibrosis or bronchiectasis.

Stridor is generally regarded as laryngeal in origin. In the presence of a normal larynx, the true cause of stridor may be found in the tracheobronchial tree. Defect in the cartilaginous framework of the trachea may permit local collapse of a segment of the trachea or bronchus during each respiratory cycle. The commonest extralaryngeal cause of stridor, however, is compression of the trachea by an abnormal aortic arch with or without malformation of the great vessels.

At the Children's Medical Center in Boston most of the tracheographic and bronchographic studies are performed with the patient under general anesthesia, following bronchoscopic examination. The iodized oil is injected via a polyethylene catheter inserted into the trachea and each lobe is filled under direction vision.—*Lois Cowan Collins, M.D.*

Abdomen

Wassner, U. J. Zur Kenntnis der Dysphagia lusoria. (On dysphagia lusoria.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin,*

June, 1957, *86*, 720–723. (Address: Justus-Liebig-Hochschule, Chirurgische Klinik, Giessen/Lahn, Germany.)

Partial compression of the esophagus by an abnormal right subclavian artery has been called dysphagia lusoria. There are other variations of vascular abnormalities which may cause the same symptoms and signs.

In the case reported by the author, there was a 2–3 cm. large filling defect in the barium filled esophagus just above the aortic knob. A right sided aortic arch was ruled out by demonstration of the arch and descending aorta on the left. In order to rule out a dilated abnormal artery, a pneumomediastinum was done. The trachea was shown to be anterior to the aorta. The aorta was situated abnormally between the esophagus and spine. The author believes this to be the first such case diagnosed before autopsy.—*Hans W. Hefke, M.D.*

Goldenberg, Ira S. Acute intrathoracic gastric dilatation associated with Bochdalek hernia in an infant. *A.M.A. J. Dis. Child*, May, 1957, *93*, 548–550. (From: Thoracic Surgical Service, Yale University School of Medicine, New Haven, Conn.)

The foramen of Bochdalek hernia is the result of a congenital defect which may become manifest in the earliest hours of life. The case of a male infant whose symptoms developed abruptly at the age of six weeks is reported. The infant's development had been entirely normal up until six weeks, at which time, shortly after the noon feeding, the child began to cry and became cyanotic and dyspneic. Chest examination revealed the dilated stomach in the left chest with a mediastinal shift to the right. Decompression was accomplished by passage of a small caliber plastic tube through the esophagus into the stomach, with resultant rapid relief of symptoms. Fluoroscopy following decompression showed normal chest and diaphragms, following which barium study demonstrated the supradiaphragmatic stomach which apparently entered the chest through a posterolateral defect in the diaphragm.

At operation a defect 3×3×2 cm., with the base on the chest wall, was found in the posterolateral portion of the diaphragm. Through it the stomach, spleen, colon and a portion of the small intestine entered the thoracic cavity. Reduction was easily accomplished and the defect repaired. The infant made an uneventful recovery.

Since the differential diagnosis in such a case lies between spontaneous pneumothorax and diaphragmatic hernia with distended gastrointestinal structures, the wisdom of avoiding needle aspiration until after insertion of nasogastric tube is stressed.—*Lois Cowan Collins, M.D.*

Ettinger, Alice, and Perez-Tamayo, Ruheri. Ulcerative jejunitis in polyarteritis. *Radiology*, May, 1957, *68*, 669–672. (Address: A. Ettinger, New England Center Hospital, Boston 11, Mass.)

The roentgen findings of an ulcerative enteritis have not previously been described in patients with polyarteritis (also known as periarteritis nodosa). This condition belongs to the group of "collagen" diseases. Since the gastrointestinal tract may also be affected, along with the other body systems, gastrointestinal symptoms are frequently present. Pathologically, the lesions found in these cases consist of infarcts, hemorrhages, ulcerations, perforations of the intestinal wall and ulcerative enteritis.

The authors report a case of polyarteritis in which barium studies of the small bowel revealed the presence of two somewhat narrowed jejunal loops which suggested the presence of an ulcerative regional enteritis. Subsequent autopsy studies showed a perforation had occurred through the wall of this involved jejunum.

The authors feel that in some obscure cases of polyarteritis exhibiting gastrointestinal symptoms, the roentgen demonstration of ulcerative lesions of the small intestines may aid in establishing the correct diagnosis.—*Donald N. Dysart, M.D.*

Brady, Boyer M., and Carroll, David S. The significance of the calcified appendiceal enterolith. *Radiology*, May, 1957, *68*, 648–653. (Address: B. M. Brady, John Gaston Hospital, Memphis, Tenn.)

During the past five years, in the John Gaston Hospital of Memphis, Tennessee, calcified appendiceal enteroliths were demonstrated by roentgenologic examination in 34 patients. Four cases are reported in detail to show (a) that demonstration of the enterolith may be of considerable help in the differential diagnosis of the acute surgical abdomen, and (b) that the incidence of perforation is greatly increased by the presence of a calcified appendiceal enterolith.

Of the 34 cases in this series, 25 were males. The age ranged from three to sixty-five years with the average being twenty years. Four patients were asymptomatic, most of the others had typical signs of acute appendicitis. Thirty-two of the 34 cases had perforation of the appendix (literature has reported up to 50 per cent). This high incidence of perforation may be explained by the average time lapse between onset of symptoms and medical consultation of three and a half days. Calcified appendiceal enteroliths are associated with appendiceal stasis and, in the presence of acute inflammation, this leads to early rupture.

The differential diagnosis of calcified appendiceal enteroliths includes right ureteral calculus, calcified lymph nodes, phleboliths, bone islands in the ilium,

gallstones, calcified arteries seen on end, calcification in a cyst, foreign bodies—e.g., opaque medication, film artefacts and skin papillomas.

The authors recommend prophylactic appendectomy in most cases where a calcified appendiceal enterolith is demonstrated, in the absence of symptoms.—*Dean Nichols, M.D.*

Ettman, Irving K., Bouchillon, C. D., and Halford, H. H. Gastrointestinal roentgen findings due to untoward effects of hexamethonium. *Radiology*, May, 1957, *68*, 673–678. (Address: I. K. Ettman, Medical Teaching Group Hospital, Memphis 15, Tenn.)

Hexamethonium is a drug which is used in the management of severely hypertensive patients. As it is a potent autonomic blocking agent it may cause gastrointestinal complications which can be serious. This report is about these complications.

Gastric retention and adynamic ileus are two of the complications that can be recognized by roentgenologic studies. The inhibited gastric motility is accompanied by a marked reduction in secretions which results in retention of food particles, which, when they adhere to the mucosa, can simulate a gastric neoplasm. Toxic amounts of the drug may also accumulate in the stomach, and, if passed irregularly into the duodenum, or vomited, will make evaluation of the dosage schedule difficult. Adynamic ileus will almost certainly occur if supportive measures such as stimulating laxatives are not given. Severe cases may easily simulate organic obstruction.

The authors feel that a simple scout roentgenogram of the abdomen can demonstrate the changes produced by the drug, frequently before clinical manifestations develop.—*Donald N. Dysart, M.D.*

Santos, Carlos. Contribution à l'étude fonctionnelle de la vesicule biliaire par la cholecystométrie. (The contribution of cholecystometry to the functional study of the gallbladder.) *Acta iber. radiol. cancerol.*, Oct-Dec., 1956, *11*, 365–415. (Address: Av. da Libertade, 11, Lisbon, Portugal.)

At the usual time after ingestion of the cholecystographic medium, the patient is fluoroscoped, and spot films of the gallbladder shadow are taken in the upright position, with graded compression, and with at least two different angles of obliquity, which is of help in the differential diagnosis of cholelithiasis. Afterwards, Bucky views of the gallbladder are taken in frontal and in straight lateral projection, with the patient in supine position, centering of the tube and cassette being facilitated by having marked the location of the gallbladder on the skin during fluoroscopy (in decubitus). From the size of the gallbladder shadow, as viewed on the roentgenograms in two incidences, one may calculate the volume of the gallbladder, with the help of a slide-rule, appropriately constructed. After the fatty meal (egg-yolk), additional films in supine profile views (with horizontal ray) are exposed after fifteen minutes, thirty minutes, one hour, and two hours. The calculated volumes are then plotted on a curve.

The author has pursued his cholecystometric studies since 1950, and has correlated the figures and the curves with clinical, laboratory, and surgical findings. As a result, he discusses normotonic situations, as well as various dyskynetic (hypertonic and hypotonic) conditions. It seems that considerable more experience will be required before the method is universally accepted. For the time being, the information yielded is hardly enough to warrant such a time-consuming procedure.—*E. R. N. Grigg, M.D.*

Levene, George, and Scheff, Saul. Intravenous cholangiography as an aid in diagnosis of carcinoma of the head of the pancreas. *Radiology*, May, 1957, *68*, 714–717. (Address: G. Levene, Massachusetts Memorial Hospital, Boston 18, Mass.)

The early diagnosis of carcinoma of the head of the pancreas is a difficult one to make as the tumor usually has to progress to the stage of causing obstruction of the common duct with the resultant production of jaundice before it is suspected. The authors describe a finding, illustrated by two case reports, which should suggest the presence of tumefaction of the head of the pancreas.

The normal common duct passes through the head of the pancreas most commonly in a downward, slightly oblique, course toward the duodenum. When the head of the pancreas enlarges it displaces the common duct which then assumes a curved form with the convexity to the right. This situation can be found following injection of cholografin which outlines the biliary tract. Laminagraphy may aid in better visualization of the ducts when overlying shadows are present.

The authors feel that this typical pattern of a displaced and deformed pancreatic portion of the common duct should aid in the early diagnosis of a carcinoma of the head of the pancreas if the history and laboratory findings rule out pancreatitis.—*Donald N. Dysart, M.D.*

Gynecology and Obstetrics

Hodge, K. E. Gravitational placentography. *Radiology*, May, 1957, *68*, 637–647. (Address: Toronto General Hospital, Toronto, Ontario.)

A gravitational method of demonstrating placental tissue situated on the lower uterine segment is described. In this method the fetus is used as a contrast medium which gravitates toward certain land-

marks. A limited number of standard roentgenographic projections are employed. Displacement of the fetus from the maternal pelvis and the uterine wall, despite the forces of gravity pulling it toward these structures, forms the basis of interpretation.

It is considered essential to follow the author's technique carefully. The patient's bladder must be completely empty, with a catheter in the bladder. The following films are exposed at a 36-inch tube film distance: an anteroposterior film of the abdomen with the table tilted approximately 45° from the vertical; a lateral film of the abdomen, with a soft-tissue filter, taken with the patient standing; a lateral film of the pelvis with the patient standing; a lateral localized film of the sacral promontory and lower lumbar spine with the table tilted approximately 45° from the vertical.

The author's study is based upon 200 consecutive cases in which there was clinically good reason to suspect placenta previa. In 36 of these a major degree of placenta previa was diagnosed roentgenologically. The diagnosis was confirmed clinically in 34. An equal degree of accuracy was achieved in the exclusion of placenta previa. Minor grades of placenta previa were diagnosed in 19 patients. The diagnosis was confirmed clinically in 7; a major degree of placenta previa was found in 2; in 10 the clinical diagnosis was indecisive.

Retrograde femoral arteriography may be used in those cases in which gravitational placentography gives doubtful results.—*Arno W. Sommer, M.D.*

Genitourinary System

Burns, Edgar, Ray, Edward H., Jr., and Morgan, James W. Bladder neck obstruction and associated lesions in children. *J. Urol.*, May, 1957, *77*, 733–740. (Address: E. Burns, 3503 Prytania St., New Orleans 15, La.)

Recent evidence has indicated that obstructive lesions of the bladder outlet are common in children. Of 129 congenital vesical neck obstructions, 123 were due to congenital hypertrophy of the internal sphincteric area, 3 to congenital valves of the posterior urethra, and 2 to congenital hypertrophy of the verumontanum. Patients with neurogenic lesions, with the exception of one type, were excluded. The one type which responds well to resection of the vesical neck is the type in which the major defect is found in the nerve fibers supplying the detrusor muscle, whereas those fibers going to the sphincteric area are intact. This results in an imbalance between the force of the detrusor and the resistance of the external sphincter and produces a vesical neck obstruction which can be remedied by surgical resection.

Symptomatology in patients with bladder neck obstruction is minimal in the early stages, and consists of urinary frequency and straining. As the lesion becomes more chronic, there is enuresis and overflow incontinence with acute retention and hematuria. Infected urine was found in 79 per cent, and 89 per cent had recurrent attacks of chills with fever.

Excretory urography will provide some diagnostic information regarding renal function and other associated anomalies of the upper urinary tract. The retrograde cystography is important to show the location of the obstruction, to outline the size and architecture of the bladder, and to indicate the presence or absence of vesicoureteral reflux. Cystography should be performed by filling the bladder through a catheter from the barrel of a 2 ounce Triumph syringe held the length of the catheter above the body level. The solution is allowed to flow into the bladder by gravity. These studies should be supplemented by cystoureteroscopic examination in all cases.

In most of the patients, the treatment is surgical removal of the primary lesion, supplemented by whatever procedure is indicated in the individual case. If the obstruction is of borderline significance in a female, urethral dilatation under anesthesia may be tried, but this method would not be suitable for the male patient. Removal of obstructing tissue may be done transurethrally or by the suprapubic transvesical approach. Most boys less than four years of age will not lend themselves well to transurethral resection. In this group the suprapubic approach is preferable. In those patients who have vesicoureteral reflux, removal of the primary obstructive lesion may be supplemented by reimplantation of one or both ureters as indicated. Patients who show severe decompensation of the upper urinary tract with hydronephrotic atrophy of the renal cortex require prolonged drainage in order to offer a maximum opportunity for a return to normal. This is done either by indwelling catheter or suprapubic cystostomy.—*George W. Chamberlin, M.D.*

Isaac, Frank, Brem, Thomas H., Temkin, Eugene, and Movius, Herbert J. Congenital malformation of the renal artery, a cause of hypertension. *Radiology*, May, 1957, *68*, 679–688. (Address: VA Hospital, 5901 East 7th St., Long Beach 4, Calif.)

The causal relationship of renal pathology to arterial hypertension is not yet clearly defined. Goldblatt presents evidence to show that interference with renal arterial blood flow through one or both kidneys can result in hypertension. There are, however, many investigators who are strongly opposed to this point of view. They contend that, with the possible exception of pyelonephric and pyonephrotic atrophy, urologic disease does not increase the incidence of hypertension. There is general agreement, however, that there are certain forms of renal disease which definitely represent the human counterpart of the experimental renal hypertension of Goldblatt. Such cases are those in which there is

marked reduction, but not complete suppression, of the arterial blood through one or both kidneys.

The authors report three cases of hypertensive disease associated with congenital malformation of one or both renal arteries. In two of these cases the malformation was unilateral. Removal of the affected kidney produced significant improvement. In the third case the vascular malformation was bilateral. One kidney was removed because of hemorrhage from anomalous renal vessels. Subsequently vascular malformations were demonstrated in the remaining kidney.

The malformation may take the form of a cirsoid angioma, giving rise to a characteristic deformity of the ureter on excretory urogram. This deformity should suggest the need for abdominal aortography by which the diagnosis can be established.—*Dean Nichols, M.D.*

Nervous System

Kirkpatrick, Rob H., and Riley, Conrad M. Roentgenographic findings in familial dysautonomia. *Radiology*, May, 1957, *68*, 654–660. (Address: R. H. Kirkpatrick, Box 202, 622 West 168th Street, New York 32, N.Y.)

Familial dysautonomia is a clinical entity characterized by a dysfunction of the nervous system with particular prominence of autonomic disturbances. It is a serious condition which manifests itself in the first few months of life and can cause marked disability. Most conspicuous symptoms and signs are excessive perspiration, drooling, transient erythematous blotching of the skin, intermittent hypertension and postural hypotension, inability to produce tears and inadequate temperature control. There may also be evidence of other dysfunction of the central nervous system. Mental retardation and convulsions are occasionally present.

The authors summarize the roentgen findings in 34 patients with familial dysautonomia. Bronchoneumonia was found in 19 of the 32 patients (60 per cent) who had roentgenograms of the chest. This was generally of a chronic nature, showing patchy increased densities in one or both perihilar regions, with extension of the process into one or two lobes. The inflammatory changes rarely involved both lungs and late emphysematous changes did not occur. Retardation in height and weight were common. Scoliosis and kyphosis and retardation in skeletal development were present in a significant number of patients. Twenty patients (60 per cent) of the children in this series had frank hypertension.

The diagnosis of this abnormality must be made from the history and the clinical findings; there are no significant laboratory findings.—*Arno W. Sommer, M.D.*

Skeletal System

Keats, Theodore E. Dysplasia epiphysialis hemimelica; (tarso-epiphyseal aclasis). *Radiology*, April, 1957, *68*, 558–563. (Address: School of Medicine, University of Missouri, Columbia, Mo.)

Dysplasia epiphysialis hemimelica is a rare epiphyseal dysplasia of the extremities. It may affect any of the epiphyses of the lower limb, and presumably the upper as well. There is an eccentric cartilaginous overgrowth of the involved ossification center. The condition is generally confined to the medial or lateral half of the epiphysis. When more than one epiphysis is involved, all the epiphyseal centers affected show overgrowth of either the medial or lateral portions. In some instances there are numerous irregular centers of ossification separate from the main epiphysis and so closely packed together that they simulate a single mass of bone. As the child grows older, these separate centers of ossification tend to fuse with each other and with the main epiphysis.

The etiology of dysplasia epiphysialis hemimelica is unknown. It is apparently a congenital error of development involving either the pre-axial or post-axial part of the apical cap of a single limb bud. There are no characteristic features on which a specific diagnosis can be made from the biopsy material. Apparently the disease is self-limited by closure of the epiphysis at puberty. Treatment is directed to correction of deformity and improvement of function.

The author presents one case of dysplasia epiphysialis hemimelica involving the left knee and ankle, to bring the total of reported cases to 29.—*A. W. Sommer, M.D.*

Define, Domingo. Deformidades raquiticas. (Rachitic deformities.) *Rev. ortop. y traumatol.*, (*Latino Americana*), March, 1957, *2*, 10–26. (From: Pavilhao Fernandinho Simonsen da Santa Casa de Misericordia, São Paulo, Brazil.)

The material used in this study consisted of 345 patients with rachitic deformities observed in the Pavilhao Fernandinho Simonsen da Santa Casa de Misericordia de São Paulo, Brazil in the interval between 1940 and 1955.

The great majority of patients were about five years of age (94 per cent). The age of the remainder varied from six months to sixteen years. One hundred and eighty-four cases were females, 161 were males; 240 of the cases were white; the remainder were of the black, Indian, and mixed Indian and white races.

Rachitic deformities are caused by an inadequate calcification of newly formed cartilage and bone and decalcification of the bone and cartilage which was calcified before the onset of the disease. As a result of these changes, the bone is soft and incompletely developed and is consequently unable to resist the normal mechanical stresses represented by the action of gravity, muscular pulls and external forces directed to the skeleton.

Rachitic deformities are found most frequently in the lower extremities. Most of these consisted of genu varum and genu valgum (93 per cent).

Other rachitic deformities encountered consisted of tibia vara, tibial defects, saber tibia, coxa vara, curvature of the bones of the forearm, kyphosis and deformities of the thorax.

The prognosis is generally good and the deformities are usually not severe. Spontaneous correction can occur with the treatment of the disease, although orthopedic manipulation may be necessary.—*Murray M. Friedman, M.D.*

Stagnara, Pierre, (Lyon), Quéneau, Pierre, (Paris), and Archimbaud, Jean, (Lyon, France.) Examen radiologique des scolioses essentielles. (Roentgen examination of essential scoliosis.) *J. de radiol., d'électrol. et de méd. nucléaire*, March-April, 1957, *38*, 149–157.

In this excellent article the authors particularly insist on the necessity of distinguishing structural scoliosis from postural scoliotic deformities. Roentgenograms taken in the recumbent position usually permit the differentiation between structural scoliosis, with its deformities persisting in the recumbent position, and the functional or postural deviations of the spine, the curvature of which completely disappears in the same position. This distinction is fundamental, because when structural scoliosis appears in a subject in the growing period, it is evolutive in practically all cases and the treatment is difficult as soon as the curvature exceeds a 30 degree angle. On the contrary, postural scoliosis is amenable to more simple therapeutic measures. It is fortunate that structural scoliosis constitutes the minority of the spinal deviations seen in orthopedic practice (1–2 per cent).

Roentgenologic study affords irrefutable differential diagnosis between postural and structural scoliosis and assures better therapeutic care. —*Maurice Dufresne, M.D.*

Fullenlove, Tom M., and Williams, A. Justin. Comparative roentgen findings in symptomatic and asymptomatic backs. *Radiology*, April, 1957, *68*, 572–574. (Address: T. M. Fullenlove, 110 El Verano Way, San Francisco 27, Calif.)

The authors present a comparative study of the roentgen findings in symptomatic and asymptomatic backs. Chosen for the survey were 200 men who denied having discomfort in the back and who had not asked for treatment for back disability at any time during their employment. For purposes of comparison, 200 consecutive patients referred for myelography were studied. Anteroposterior and lateral roentgenograms of the entire lumbar spine and a spot roentgenogram of the fifth lumbar vertebra were made. All abnormalities were reported in the following classifications: congenital, traumatic, degenerative, inflammatory, arthritic, neoplastic, and structural.

Congenital lesions of the back were found to have essentially the same incidence in symptomatic and asymptomatic patients, and old traumatic lesions of the spine were also evenly distributed. Of the degenerative changes, narrowed disks with spurs showed a much higher incidence in patients having symptoms. There was no significant difference in the incidence of other degenerative lesions. Arthritis occurred in a definitely greater percentage of patients with symptoms than of those without symptoms.

It is concluded that congenital lesions are not a source of symptoms either in the presence of injury or apart from it, and that the practice of attributing symptoms to such lesions is not valid.—*Arno W. Sommer, M.D.*

Isemein, L., and Fournier, André-M. (Marseille, France.) Images carpiennes du début de la polyarthrite. (Carpal images at initial stages of polyarthritis) *J. de radiol. et d'électrol. & Arch. d'électric. méd.*, Nov.-Dec., 1956, *37*, 869–876.

The authors report 7 proved cases of primary progressive chronic polyarthritis. These patients are all women from twenty to forty-four years of age (mostly around or below thirty). The accompanying fine carpal roentgenograms of each are discussed and characteristic changes of the initial stage of the disease pointed out. These are: loss of calcium, osseous atrophy, bone texture changes (such as stippling, osteosclerosis of trabecular patterns, microcyst formations), erosion of borders of bones with narrowing of joint spaces and slight ulnar slipping of the carpal bones and finally soft tissue changes. Most of these roentgen findings were noted before the clinical onset of the disease and according to the authors, even though not pathognomonic, they were clear signs to warrant suspicion of pathology, vindicated by subsequent developments and clinical observations.—*Jirair N. Sarian, M.D.*

Jacqueline, F. (Aix-les-Bains, France.) Troubles de la structure osseuse et lésions destructives au cours de la spondylarthrite ankylosante. (Bone texture changes and destructive lesions in various stages of ankylosing spondylarthritis.) *J. de radiol. et d'électrol. & Arch. d'électric. méd.*, Nov.-Dec., 1956, *37*, 887–893.

Clinical, roentgen and laboratory findings of 8 cases are reported. Five of these are grouped together manifesting the early stage of the disease. The progressive changes noted were radiolucent zones at

vertebral borders anteriorly, with effacement, then either reappearance of these borders, giving the body a square appearance (on the lateral view) or formation of bases of osteophyte bridges anteriosuperiorly and anterioinferiorly. Concomitantly osteoporosis of vertebrae and clear-cut ankylosis of the apophyseal articulations were demonstrated. The author is of the opinion that these early destructive changes are not only transient, but are apparent and are due to intense osteoporosis and subsequent peripheral osteosclerosis and final bony ankylosis. However, he states that in certain rare cases there are real destructive lesions involving the spine and the hips.

The remaining 3 cases are discussed together as advanced and well stabilized cases (multiple vertebral bony bridges), which, however, showed localized destructive lesions (compression) after trauma. The process of development of these destructive lesions is definite as compared to the ones described above as indicative of the early stage of the disease. However, the osteoporosis and all of these destructive lesions both in the spine, sacroiliac and hip articulations can be explained by an underlying vascular pathology (as evidenced by thickening of arteries, plasmostasis and fibrotic changes in the spinal cord) of unknown origin.

In addition, the author presents 3 other cases of hip ankylosis in severe spondylarthritis ankylopoetica. These cases also show diffuse osteoporosis of the pelvis and of the spine and ankylosis of the apophyseal articulations.

Ankylosis of the sacroiliac articulations and the intervertebral bony bridges are indicative of late stages of spondylarthritis ankylopoetica. The first changes noted at both articulations are small zones of subchondral osteoporosis involving the sacral as well as iliac components, thereby causing some irregularity of the articular borders and, at times, slight widening of the articular space. These changes are followed by alternating zones of osteosclerosis of the articular borders. Subsequently as the changes extend, there is loss of articular line leading finally to complete bony ankylosis of the joints. Analogous changes can be noted at the apophyseal articulations and in severe cases at both hips.—*Jirair N. Sarian, M.D.*

O'Donoghue, Don H. (Oklahoma City, Okla.) Impingement exostoses of the talus and tibia. *J. Bone & Joint Surg.*, July, 1957, *39-A*, 835–852.

The author presents a thorough discussion of talotibial impingement exostoses. These are formations of osteochondromatous ridging just above the anterior lip of the lower articular surface of the tibia and on the opposing area of the neck of the talus. This same type of lesion may develop in other areas around the ankle.

In extreme dorsiflexion of the foot the anterior tibial lip fits into the sulcus on the top of the talus between the head and body. There are no true ligamentous attachments at either location.

Spur formation occurs as a result of forced dorsiflexion of the foot as observed during "drive" in an athlete. This starts a vicious cycle since the greater the bone formation the more easily impingement will occur. Roentgenograms show that the anterior margin of the tibia is sharp, rather than rounded, with shelf formation extending along the width of the bone. The neck of the talus may show an opposing spur. In the early stages these are small, but may later be huge. Broken spurs will be found as loose bodies. Similar spurring may form on the medial and lateral maleoli. The author believes these are unlike marginal osteophytes which are associated with degenerative changes.

When severe, the impingement exostoses may preclude athletics. The patients lose their "drive" but may have rather vague complaints. The one essential clinical finding is pain on forced dorsiflexion of the foot located at the anterior talotibial sulcus. There is no swelling.

One hundred and twenty athletes and 120 non-athletes were studied and it was found that exostoses were absent in 84 per cent of the non-athletes, but in only 55 per cent of the athletes; 27.5 per cent of the athletes showed both talar involvement, but only 3 per cent of the non-athletes had opposing spurs. There was also a decided difference in the size of the exostoses which averaged larger in the athletes and gave more symptoms.

Apparently the reaction is initiated by the repeated mild trauma of direct impingement. Restriction of activity will relieve symptoms. If function is sufficiently impaired, surgical removal is indicated. The author's surgical approach is usually anterolateral, but occasionally an additional incision is necessary medially or posteriorly. The operative procedure is described and there are detailed clinical records and roentgenograms of fair quality for his surgically treated cases, and 4 cases treated conservatively. They obtained 6 excellent and 2 good results in 8 operations. The spurs have not recurred postoperatively—*Martha Mottram, M.D.*

Lichtenstein, Louis. Aneurysmal bone cyst; observations of fifty cases. *J. Bone & Joint Surg.*, July, 1957, *39-A*, 873–882. (From: The Department of Pathology, Wadsworth General Hospital, Veterans Administration Center, Los Angeles, Calif.)

The author reports on 50 cases of aneurysmal bone cysts, 33 of which have not been reported previously.

Aneurysmal bone cysts have been found in almost every bone. The most common sites were the long bones and the vertebrae (60 perc ent in this series). Cervical and lumbar involvement was more common

than thoracic. There was no sex predilection. Two-thirds of the present cases were in children or adolescents.

The article deals more with treatment than with the details of diagnosis but many roentgenograms are included. The bone is expanded, often eccentrically, and is cystic in appearance.

The danger with untreated cysts is that they may attain large size, even enough to necessitate amputation, or in the vertebrae, to result in paraplegia. Vertebral lesions may enlarge quite rapidly and extend to contiguous vertebrae.

For surgically accessible lesions of small or moderate size, the author recommends curettement and packing with bone chips. Unless curettage is thorough, the lesion may recur. For deep seated lesions in inaccessible sites, such as the vertebrae, roentgen therapy is advised. When curettage is incomplete it should be supplemented with roentgen-ray treatment. A total dose of 1,400 r is suggested for effective control. Doses exceeding 2,000 r should be avoided because of the danger of development of sarcoma at a later date.—*Martha Motttram, M.D.*

Rowe, Caroline W., and Haggard, Mary E. Bone infarcts in sickle-cell anemia. *Radiology*, May, 1957, *68*, 661–668. (Address: University of Texas, Medical Branch, Galveston, Texas.)

Two cases of sickle-cell anemia accompanied by destructive bone lesions are reported. In both cases outstanding features were the clinical and roentgenologic evidence of bone involvement. In the first case, the bone lesions were easily attributable to sickle-cell anemia; other conditions were readily excluded by the history and serologic findings. In the second case, the presence of infection and the culturing of Salmonella typhi murium from an abscess made the diagnosis of uncomplicated bone infarct somewhat less positive.

Infarction in sickle-cell anemia has long been recognized, and aspetic necrosis has been described in virtually every organ and tissue in the body. Bone infarcts have received less attention in the literature than other features of this disease. There appears to be considerable confusion in the interpretation of bone changes. In some instances the bone changes have been diagnosed as osteomyelitis. Although staphylococcal osteomyelitis in addition to sickle-cell anemia has been reported, it is more common to find no exudate when the bone is exposed and to obtain sterile cultures.

It is postulated that many cases of bone infarction in individuals with sickle-cell anemia go unrecognized either because no roentgenograms are made, or because of an insufficient interval between the onset of symptoms and roentgen examination. An interval of two to three weeks apparently must elapse before the roentgenographic changes become evident. The initial bone involvement consists of patchy areas of destruction in the spongiosa with periosteal reaction. Subsequently there appears to be a complete rebuilding of the shaft, while the original shaft is ultimately completely absorbed.

In the early stages the bone changes may be identical with those seen in osteomyelitis, congenital syphilis, metastatic malignant disease, Ewing's sarcoma, leukemia or tuberculosis. If it is known that the patient has sickle-cell anemia, one should be alert to the possibility that the condition may be uncomplicated bone infarct.—*Arno W. Sommer, M.D.*

Vollmar, K. Über das Vakuumphänomen an den Randleisten der Lendenwirbel. (The vacuum sign in the ossified secondary centers of the lumbar vertebrae.) *Radiol. clin.*, March, 1957, *26*, 75–79. (Address: Strahleninstitut der Allg. Ortskrankenkasse, Machabäerstrasse 19–27, Köln, Germany.)

While the vacuum sign in degenerative diseases of the intervertebral disks is not at all uncommon, a similar phenomenon seen on the anterior, superior and inferior edges of the ossified secondary centers are much less common. The author reports three such cases. They may easily be overlooked, because they are small and sometimes only pin-point in size. The visibility of the vacuum is often improved by dorsiflexion of the spine. Degenerative changes in the cartilaginous ridge are probably the cause for the unusual findings.—*Hans W. Hefke, M.D.*

Williams, D. Innes, and Nixon, H. H. Agenesis of the sacrum. *Surg., Gynec. & Obst.*, July, 1957, *105*, 84–88. (From: The Hospital for Sick Children, Great Ormond Street, London, England.)

The authors divide sacral agenesis into two groups. In the first there is agenesis without anorectal anomaly and they studied 8 patients with this deformity. None had more than three sacral segments and all proved to have neurogenic disorder of bladder function. Severe constipation with absence of the normal sense of bladder distention was also common. There was curiously little external deformity although several had minor abnormalities of the feet and one had a paralyzed leg with dislocation of the hip.

In the second group there is sacral agenesis with anorectal anomaly. When the anorectal anomaly was low, in about one-half the cases there was true sacral agenesis but when the anomaly was high with the bowel ending above the pelvic floor, true sacral agenesis was less common.

No case seen by them with agenesis of more than one sacral segment escaped without bladder disorder.—*Arthur E. Childe, M.D.*

Kamieth, H. Was leisten gezielte Spaltaufnahmen der Ileosakralgelenke? (Ein Beitrag zur Pathologie der Ileosakralgelenke). (What

do spot films of the sacroiliac joints have to offer? [A contribution to the pathology of the sacroiliac joints].) *Radiol. Clin.*, May, 1957, *26*, 139–157. (Address: Strahleninstitut der Universität, Homburg [Saar], Germany.)

The anatomic structure of the sacroiliac joints is rather complicated and irregular. Different types of special views have been used for a better visualization, in addition to the routine roentgenograms of the pelvis. The author employs a spot film technique after fluoroscopic selection of the best position, which is an oblique tilted pelvis view, designed to open the joint space maximally on the film.

Degenerative arthrosis is fairly common, but usually of little clinical significance. Osteitis condensans ilei can be demonstrated much more accurately by special films of the sacroiliac joints. Injury to the cartilage and band apparatus seems to be responsible for the bony changes adjacent to the joint, occurring after parturition. Static changes as in scoliosis may cause unilateral chronic osteitis. In inflammatory lesions, as tuberculosis, the special film technique contributes considerably to accurate visualization of the lesion. Spondylitis rhizomelique and its early involvement of the sacroiliac joints may be difficult to diagnose on routine films; the open joint film adds considerable help in the diagnosis.—*Hans W. Hefke, M.D.*

Blood and Lymph System

Müller-Mohnssen, H. Die Koronarsklerose im postmortalen Arteriogramm. (Coronary sclerosis in postmortem arteriography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, May, 1957, *86*, 539–556. (Address: Physiol. Inst. d. Univ. des Saarlandes, Homburg/Saar, Germany.)

Because of rapid advances in cardiac surgery, it becomes important to obtain more detailed information about the coronary vessels. Accurate data during *in vivo* studies are rendered difficult, not only because of movements of the heart, but also because the finer branches of the coronary vessels may not be satisfactorily opacified. For the best results in postmortem examinations, stereoscopic roentgenograms are required after injection of the coronary circulation with 40 per cent iodipin (Merck).

There are many variations in the number, site of origin, and distribution of the coronary vessels. The right coronary artery is extremely variable in its site of origin, but usually divides into 2 broad branches very quickly. The left coronary artery displays considerable variability in its subdivisions, in which dichotomy is common, trichotomy is fairly frequent, and quadrichotomy may occur although rarely. A "right-sided distribution" consists of a normal right coronary artery, which supplies the posterior wall of the left ventricle aided by a well developed left marginal ramus. The "left-sided" type consists of a left coronary artery giving rise to a broad posterior descending ramus to supply the entire septum from the left side. After coronary occlusion it is sometimes extremely difficult to determine whether the existing blood supply is of the so-called primary congenital type or of the secondary acquired type. The former type is more likely if the findings are as follows: the supply of the anterior wall is normal and the supply of the posterior wall is a variant; arterial branches come off at an angle of less than 90 degrees (the vertex of the angle faces its artery of origin). An increase in the number of branches off the left coronary artery indicates a "left-sided" type, whereas dichotomy near the main trunk of the left coronary artery indicates a "right-sided" congenital type or a normal distribution with right-sided preponderance.

Postmortem studies of the coronary circulation have also elicited considerable information about pathologic processes. Myocardial dilatation is characterized by an increase in the number of long and narrow vessels within a large section of the heart which is relatively pale. In myocardial hypertrophy, the vessels show an increase in caliber within the hypertrophied chamber of the heart. Muscular atrophy consists of involution of cardiac muscle more intense than the decrease in the number of vessels, thereby causing considerable kinking and curling of the vessels. Vascular hypertrophy leads to a generalized increase in the number and caliber of the vessels. Senile ectasia, probably a forerunner of arteriosclerosis, represents a type of cylindrical aneurysmal formation and is due to severe local disturbances of the vascular wall. Arteriosclerosis most often begins in the left descending ramus of the left coronary artery and is responsible for most cases of coronary insufficiency, myocardial infarction, and sudden death. In fresh thrombosis, the contrast material forms a concave border against the thrombus; in older thromboses, the border is convex; in a mural thrombus, the border is somewhat pointed but generally concave when there is occlusion, or the border is smooth and semicircular when the vascular channel is open. Thus a fresh occlusion can be postulated on the basis of a concave border of the contrast material and a relative absence of peripheral vessels. Similarly, an old occlusion can be diagnosed by the convex border and the well-developed collateral circulation.—*Joseph Zausner, M.D.*

Stabert, Ch., Nicol, M., and Tacher, J. (Rennes, France.) Exploration angiographique des anévrysmes artério-veineux sous-claviers d'origine traumatique. (Angiographic exploration of subclavian arteriovenous aneurysms of traumatic origin.) *J. de radiol. et d'électrol. & Arch. d'électric. méd.*, Nov.-Dec., 1956, *37*, 883–886.

The authors report a case of subclavian arteriovenous aneurysm and fistula due to a hand grenade

wound. This was clearly demonstrated by means of arteriography conducted during surgery for correction. The arterial and venous routes used were not adequate, whereas 20 cc. of 70 per cent diodone injected into the innominate artery gave very good visualization of the subclavian artery, of the arteriovenous aneurysm and fistula and of the superior vena cava and right innominate vein. During the injection of this contrast medium the axillary and the carotid veins and arteries were manually compressed and thus a good concentration of the contrast medium was obtained at the site of the fistula.

A few angiograms visualizing the aneurysm and arteriovenous fistula accompany the article. Postoperatively, the fistula could not be demonstrated, thereby showing the double value of such a procedure.—*Jirair N. Sarian, M.D.*

Hudson, Granville W. Venography in superior vena caval obstruction. *Radiology*, April, 1957, *68*, 499–506. (Address: Vanderbilt University Hospital, Nashville, Tenn.)

Venography provides roentgenographic visualization of the superior vena caval system and offers a reliable means of obtaining precise information regarding the anatomic site and degree of obstruction in lesions of these veins. The procedure also demonstrates the pattern and extent of the collateral channel formation around the sites of obstruction in the superior vena cava. This information is essential if surgical treatment is contemplated.

Superior vena caval obstruction may be caused by a variety of mediastinal abnormalities. The most common tumors involving this region are: bronchogenic carcinoma; malignant lymphoma; mediastinal fibrosarcoma; carcinoma of the mediastinal lymph nodes, metastatic from the breast, thyroid, and pancreas. Other causes include aneurysms, chronic fibrous mediastinitis, and thrombus formation.

The author describes the technique which he utilized to study lesions producing obstruction in the superior vena caval system. He reports two illustrative cases. For venography in this series a rapid cassette changer that allows exposures to be obtained at intervals of one second was utilized. Diodrast, urokon or neo-iopax was injected rapidly into an arm vein, and serial roentgenograms were obtained. The first film was exposed toward the end of the injection.

In one of the reported cases, venograms demonstrated a large filling defect involving the medial aspect of the superior vena cava and permitted identification of the collateral circulation around the block. Exploration of the thorax disclosed adenocarcinoma of the bronchus extending posteriorly to encircle the superior vena cava. Cicatricial changes, thought to be the result of an old tuberculous lymphadenitis, were responsible for obstruction in the other reported case.—*Arno W. Sommer, M.D.*

Süsse, H. J., and Radke, H. Nachweis und Lokalisierung von Nebennierentumoren mittels Aortographie. (Diagnosis and localization of adrenal tumors by means of aortography.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, May, 1957, *86*, 599–604. (Address: Universitäts-Röntgeninstitut, Liebigstr. 20 a, Leipzig C 1, Germany.)

The authors describe 3 patients in whom the diagnosis and localization of an adrenal tumor were made by means of lumbar aortography. This procedure was tried when retroperitoneal insufflation combined with laminagraphic studies failed to give a definitive diagnosis. For this purpose, a diagonal puncture of the aorta is made at the level of T-11 or T-12 under general anesthesia. The authors parenthetically suggest that catheterization of the femoral artery to the same level is probably less dangerous.

The diagnosis of adrenal tumor is made by the increased vascularity or by the increase in opacification within the tumor.—*Joseph Zausner, M.D.*

General

Nägele, E. Röntgenbefunde bei progressiver Sklerodermie. (Roentgen findings in progressive scleroderma.) *Radiol. clin.*, Jan., 1957, *26*, 1–12. (Address: Röntgenabteilung der Medizinischen Poliklinik, Giessen, Germany.)

These studies are based on roentgen examinations of 10 patients with scleroderma.

Roentgenograms of the lungs showed a reticular pattern of the lower lung fields as a sign of early fibrosis. Later on the fibrosis spread to the middle lungs. Changes of the pleura, especially near the diaphragm, and pleuropericarditis were observed. Lung changes led to chronic bronchitis, bronchopneumonia and bronchiectasis.

The heart showed fibrosis of the myocardium. Pericarditis obliterans was seen. Cor pulmonale secondary to lung fibrosis was also noted.

The walls of esophagus, stomach and intestines showed fibrosis with damage to the muscular layers. The esophagus gave the appearance of a rigid, air-filled sac with little or no peristalsis and narrowing of its lowest portion. Insufficiency of the cardia with regurgitation from the stomach and sometimes secondary esophagitis and ulcer were seen.

The stomach with its rigid walls and little peristalsis sometimes resembled linitis plastica. In the small intestines, large collections of barium in dilated loops were seen, and the colon showed large saccular as well as narrowed portions. Colicky pain, sometimes with vomiting and even complete ileus occurred.

Deposits of calcium carbonate and calcium phosphate were found in the soft tissues, in the annulus fibrosus of the heart and in the capsule of the liver and spleen.

Characteristic changes of the skeleton were general osteoporosis and the well-known osteolytic defects of the tips of the distal and middle phalanges of the fingers and toes.

Of the circulatory system, besides the heart, the blood vessels showed pathologic changes.

The author's conclusions from these examinations are: Progressive scleroderma is a disease of the connective tissue system causing changes in numerous organs, some of them giving characteristic roentgen-ray findings. Thorough roentgen examination in all cases of progressive scleroderma is indicated.—*Hans Lewin, M.D.*

Fischer, Harry W. Colloidal stannic oxide; animal studies on a new hepatolienographic agent. *Radiology*, April, 1957, *68*, 488–498. (Address: University Hospitals, State University of Iowa, Iowa City, Iowa.)

The author first compares the radiopacity of stannic oxide with that of iodine and thorium in lucite phantoms, and finding it comparable, used it in 8 separate intravenous injections in 4 dogs, and 27 separate injections in 13 rabbits. The particle size was mainly 1 micron or less with none over 2 micra. The substrates, varying slightly above and below pH 7 with some containing 25 per cent sucrose, made no detectable difference in toxic reactions or organ uptake. The colloidal suspensions of tin oxide were prepared in concentrations of 10 and 20 per cent weight/volume of tin, with the injected dose of tin being about 350 mg./kg. Twice this amount was also well tolerated.

Rabbits and dogs were sacrificed subsequently and gross and microscopic studies of the liver, spleen, lung and kidney were performed. Pathologically, the liver and spleen were slightly lighter in color than usual, with the histopathologic section showing deposition of pigmented granules in the reticuloendothelial cells of these organs. Occasionally some granules were seen in lungs, adrenals, and kidneys. In no instance was there any tissue or cell reaction detected due to the engulfed tin.

Maximum (and excellent) opacity of the spleen and liver was obtained in 4 hours or less. Increased radiopacity occurred with succeeding doses until all the reticuloendothelial cells were saturated. There was no decrease in radiopacity of the liver or spleen at the time of sacrificing the animal. One pregnant rabbit showed placental uptake of the tin. In two rabbits rather poor opacification of the liver of a spotty nature was obtained and both these animals proved to have a diffuse involvement by coccidia in this organ (demonstrated on autopsy). Eighty kvp. conventional technique, as well as lower kvp. techniques, was adequate for this study. Absolutely no toxicity of any kind was found, with the exception of one rabbit that died from a grossly bacterially contaminated dose. Total doses up to 1,578 mg./kg. of body weight were tolerated without adverse effect. All animals gained weight showing no abnormality.

The author demonstrated that tin fulfills the requirements of Thomas for the ideal hepato-lienographic agent except for the last, vis: "if possible, (the agent) should be safely and rapidly eliminated from the body," since, as far as is known, tin remains permanently in the reticuloendothelial cells. Further studies are contemplated.—*Dean Nichols, M.D.*

RADIATION THERAPY

Schirren, Carl Georg. Über eine gefahrlose Röntgenepilation des behaarten Kopfes. (A safe roentgen epilation of the head.) *Strahlentherapie*, Nov., 1956, *101*, 393–399. (From: Dermatologische Klinik und Poliklinik der Universität, München, Germany.)

Both experimental (to small fields) and clinical (in a small epidemic of microspore infection) results demonstrated that radiation effect on hair follicles is additive, even when the total dose is fractionated over as much as twelve days. Whether an epilation dose of 375–400 r at 50 kv. and 30 cm. focal skin distance with 1 mm. Al filter and half-value layer of 0.9 mm. Al, to each of 4 cranial fields (occipital, frontal and 2 temporal) was administered at a single sitting or fractionated into five 77 r doses, or eight 50 r doses made no difference in the final result. All these modes of treatment yielded epilation approximately two weeks after the last treatment, and all had normal regrowth of hair. In the meantime, fractionation had the advantage of less biologic effect on skin and brain (no electro-encephalographic changes in patients whose treatment was fractionated, while single dose methods have been shown to cause electro-encephalographic changes).

In sum, fractionated roentgen therapy is simply additive for the hair follicles, while for other structures, the biologic effect is less than simple summation.—*Henry G. Moehring, M.D.*

Berman, Harry L. Immobilization of the head during rotational x-ray therapy. *Radiology*, April, 1957, *68*, 579–581. (Address: Walter Reed Army Hospital, Washington 12, D. C.)

The author describes a head-immobilizing device for rotational roentgen therapy. It consists of a chin rest and a vertex support, designed to hold the head in a fixed position after accurate beam localization. Cooperation of the patient is still essential but unintentional change in position is prevented.—*Arno W. Sommer, M.D.*

Becker, Josef, and Weitzel, Günter. Dreijährige Erfahrungen mit dem 15 MeV-Siemens-Betatron. (Three years' experience with the 15 mev. Siemens betatron.) *Strahlen-*

therapie, Oct., 1956, *101*, 167–179. (From: Czerny-Krankenhaus für Strahlenbehandlung der Universität, Heidelberg, Germany.)

During their 3 years of experience with the 15 mev. Siemens betatron, the authors administered some 22,600 radiation treatments—both with electron beam and with ultra-hard roentgen ray beam. They present a series of illustrations of therapeutic results in selected patients.

The outstanding characteristic of the *electron beam* is the abrupt drop in dose beyond the depth of maximum dosage. With the 15 mev. betatron, therapeutically effective doses (arbitrarily set at 50 per cent of the maximum dose) extend to about 6 cm. depth. Thus the electron beam is particularly applicable to treatment of the relatively superficial tumors—most tumors about the head, including peripherally located cerebral tumors; metastases to cervical, supraclavicular, axillary and inguinal lymph nodes; tumors of the skin, larynx, pharynx, vulva, urethra and penis; and the superficial spreading type of mammary carcinoma.

The usual, daily dose varied from 300 to 500 r, depending on the size of the field, to a total dose of 5,000 to 6,000 r. If the goal of complete regression of tumor is not reached, another series of 4,000 r is given in eight weeks. This occurs frequently in melanomas. Small fields tolerate as much as 10,000 to 12,000 r.

The *ultra-hard roentgen ray* beam is most useful in treatment of deep-seated tumors: bronchial and other pulmonary tumors; renal and bladder tumors; gynecologic and other abdominal tumors. Daily tumor doses of 200 r to a total dose of some 6,000 r are a reasonable aim in this type of therapy.

Results thus far justify further exploitation of betatron therapy.—*Henry G. Moehring, M.D.*

Becker, Josef, and Weitzel, Günter. Neue Formen der Bewegungsbestrahlung beim 15 MeV-Betatron der Siemens-Reiniger-Werke. (New forms of pendulum irradiation with the 15 mev. betatron of the Siemens-Reiniger Werke.) *Strahlentherapie*, Oct., 1956, *101*, 180–190. (From: Czerny-Krankenhaus für Strahlenbehandlung der Universität, Heidelberg, Germany.)

The authors present a series of diagrams and photographs to illustrate the theory and application of an attachment which permits pendulum therapy with the Siemens 15 mev. betatron. Depth dose distributions are also considered.—*Henry G. Moehring, M.D.*

Becker, Josef, Weitzel, Günter, and v. d. Decken, Claus Benedict. Die Gittermethode bei der Strahlenbehandlung mit ultraharten Röntgenstrahlen von 15 MeV. (The grid method in radiation therapy with ultra-hard roentgen rays at 15 mev.) *Strahlentherapie*, Oct., 1956, *101*, 191–196. (From: Czerny-Krankenhaus für Strahlenbehandlung der Universität, Heidelberg, Germany.)

The half-value layer for ultra-hard roentgen rays generated at 16 mev. in a betatron is 16 mm. of lead, so the authors had to construct a lead grid 48 mm. thick to get reduction of dose behind the shielded areas to 12.5 per cent of the incident dose. The grid effect is achieved by truncated conical holes, approximately 4 mm. in diameter, bored through this lead at such intervals that the shielded areas were in a 60:40 ratio to the open areas. Depth dosage distribution obtained from measurements in a phantom showed no homogenization of the beam beneath the grid; *i.e.*, even at 25 cm. depth, the relationship of the dose under shielded areas to that under the open areas remained as 42:100. The authors used 4 narrow light beams to align the betatron, the grid and the treatment fields for each treatment.

Not enough time has elapsed to permit more than speculation about clinical results. However, just as grid therapy with conventional roentgen rays has a skin-sparing effect, so grid therapy with ultra-hard rays has a tissue-sparing effect. The speculation about clinical value of grid therapy with ultra-hard roentgen rays turns about this point—perhaps some therapeutic value results from sparing tissue in and about the tumor bearing area. An obvious advantage of grid therapy is the ability to irradiate larger fields because of the tissue-sparing effect. Just what clinical benefit this will produce remains undetermined. —*Henry G. Moehring, M.D.*

v. d. Decken, Claus Benedict. Tiefendosiskurven bei der Bestrahlung mit schnellen Elektronen in Abhängigkeit von der Energie und der Feldgrösse. (The dependence of depth dose on energy levels and field size in irradiation with an electron beam.) *Strahlentherapie*, Oct., 1956, *101*, 204–207. (From: Czerny-Krankenhaus für Strahlenbehandlung der Universität, Heidelberg, Germany.)

The author measured depth doses for an electron beam at different energy levels and with different field sizes (from 3 to 15.6 mev. and from 2 to more than 7 cm. diameter) in a water phantom with an ionization chamber 2 mm. thick and 10 mm. in diameter. He presents his results in the form of 6 sets of curves.—*Henry G. Moehring, M.D.*

Seaman, William B., and Ackerman, Lauren V. The effect of radiation on the esophagus; a clinical and histologic study of the effects produced by the betatron. *Radiology*, April, 1957, *68*, 534–541. (Address: W. B. Seaman,

Presbyterian Hospital, 630 W. 168th St., New York 32, N. Y.)

Medical literature contains relatively little information about the effects of radiation on the esophagus. Few injuries of this structure have been recorded and consequently its sensitiveness has not been subjected to experimental investigation. Since the advent of supervoltage therapy there is greater need for knowledge regarding the dose that the esophagus and other organs can tolerate.

The authors have found that a major limiting factor in the treatment of intrathoracic cancer with the betatron has been the tolerance of the esophagus. In their series of cases of carcinoma of the lung treated with the betatron there were 20 who could not be adequately treated without inclusion of the esophagus within the irradiated volume. All exhibited clinical evidence of radiation esophagitis. In 11 patients, the reaction was considered to be mild, consisting of slight to moderate substernal burning. Four experienced moderately severe reactions, characterized by more severe pain on swallowing and lasting for two or three months after the end of therapy. Five severe reactions were manifested by marked dysphagia and the development of permanent strictures requiring dilatation. In two patients, a tracheo-esophageal fistula developed. The time of the appearance of the dysphagia varied from the twelfth to the thirtieth day of therapy, after the esophagus had received doses varying from 2,000 to 2,500 r in two weeks to 4,000 to 4,500 r in four weeks.

It is concluded that the maximum tolerance dose over the esophagus is a total of 6,000 r given at a rate of 1,000 r per week.—*Arno W. Sommer, M.D.*

von Saal, Hermann, and Dalicho, Wilhelm Albrecht. Frühergebnisse der Röntgentherapie von Hauttumoren bei lokaler Sauerstoffzufuhr. (Early results from treatment of skin tumors with radiation supplemented by local application of oxygen.) *Strahlentherapie*, Jan., 1957, *102*, 31–42. (From: Röntgen- und Strahleninstitut und Strahlenklinik der Stadt Gera, Gera, E. Germany.)

Previous experimental investigations by a variety of workers demonstrated that: (1) Oxygen lack appears to have a great practical significance in the development and growth of malignant tumors; (2) many tumors are oxygen-sensitive. In these, the critical oxygen pressure seems to be higher than 2.5 atmospheres; (3) the addition of oxygen increases radiation sensitivity up to an oxygen concentration of approximately 21 per cent; (4) the addition of oxygen selectively increases radiation sensitivity of tumors, without change in normal tissues, because of the oxygen and blood supply to tumors (which is usually considerably lower than that of normal tissue).

Comparison of results from three to twelve months after treatment showed that the addition of oxygen permitted reduction of radiation dose by about 50 per cent. Thirty-two carcinomas of the skin were treated by radiation (average dose of 3,000 r) and oxygen (oxygen was injected into the tumor and its surroundings, and the tumor, if ulcerated, was bathed in a stream of oxygen, just before administration of radiation). The control group consisted of 112 similar tumors treated with radiation only (average dose of 6,500 r). The fractionation of this radiation was, in general, greater for those tumors treated with supplemental oxygen. All radiation was generated at 60 kv., 4 ma., with a focal-skin distance of 3 to 5 cm.—*Henry G. Moehring, M.D.*

Nice, Charles M., Jr., with the technical assistance of John Kuntz. Relation of tumor size to radioresistance. *Radiology*, April, 1957, *68*, 555–557. (Address: C. M. Nice., Jr., University of Minnesota Medical School, Minneapolis 14, Minn.)

The results of experiments to determine the relation of tumor size to radioresistance are reported. Groups of mice with tumors of various sizes (0.8 to 2.2 cm. in diameter) were treated with single doses of 200 to 1,000 r. The tests were carried out in a large number of transplant generations extending over a period of two years. In measuring the response to irradiation, the end point selected was survival of the host with no evidence of tumor two months after irradiation. These mice were considered cured.

There was a definite tendency for the larger previously untreated tumors to be more resistant to irradiation than smaller previously untreated tumors. These findings are in accord with clinical observations of human subjects with leukemic and other lymphomatous masses treated by irradiation.

In mouse tumors measuring from 0.8 to 1.4 cm., increase of the dose from the 200 to 400 r range to the 450 to 800 r range, doubled the percentage of tumors eradicated. This may lend credence to the idea of giving the maximum safe dosage in clinical radiation therapy to apparently localized lymphomatous masses.—*Arno W. Sommer, M.D.*

RADIOISOTOPES

Schinz, H. R. Ergebnisse der Strahlenbehandlungen von Harnblasengeschwülsten. (Results of irradiation of urinary bladder tumors.) *Fortschr. a. d. Geb. d. Röntgenstrahlen u. d. Nuklearmedizin*, March, 1957, *86*, 363–373. (From: Radiotherapeutische Klinik des Kantonsspitals, Zürich, Switzerland.)

This report is based upon irradiation of tumors of the urinary bladder of 25 women, average age 59.1 years, and 96 males, average age 62.6 years. Papillomas and noninfiltrating superficial carcinomas were

treated with radioactive cobalt—a solution of $CoCl_2$ in water. The infiltrating and more extensive carcinomas were treated with betatron irradiation.

The $CoCl_2$ solution was injected into the intravesical balloon of a Bardex-catheter. Since the β rays were absorbed by the rubber wall of the balloon, only the γ rays of the radioactive cobalt amounting to 96 per cent of the spectrum, were effective. The 18–25 mc Co^{60} used produced 800–1,200 r in twenty-four hours at the circumference of the balloon. The intention was to irradiate with a dose of 10,000 to 12,000 r which necessitated continual treatment lasting eight to ten days. Since at a distance of less than 2.5 m. (8 ft. 4 in.) the daily tolerance dose was greater than 50 mr, nurses of older age were assigned for attending the patient during the time. Position and filling of the balloon were controlled by roentgenography. Sodium iodide was added to the cobalt solution to obtain the necessary contrast for roentgenography.

A table shows the generally good results of radioactive cobalt therapy in benign papillomas. It was tried also in malignant papillomas and large superficial carcinomas, with additional betatron irradiation used only in case of recurrence. The results were naturally less favorable than in benign tumors.

As a whole, however, the results in the series of malignant tumors were considerable. As an example, 3 cases of carcinoma of the bladder are shown by illustrations, before and after betatron irradiation. One table shows the remarkable results of palliative betatron therapy in large, malignant bladder tumors.

The intravesical radioactive cobalt therapy is for the patient a very exhausting and dangerous procedure due to frequent and long-lasting secondary cystitis. On the other hand, results of betatron irradiation were beneficial even in malignant tumors. For this reason, the author decided to abandon the radioactive cobalt therapy and to use in the future betatron irradiation exclusively, even in benign and superficial bladder tumors.—*Hans Lewin, M.D.*

Harel, J., Guérin, M., Tubiana, M., and Abbatucci, J. Production de tumeurs malignes (hépatomes et autres) par injections intrapéritonéals d'or radioactif chez le rat blanc. (Production of malignant tumors [hepatomas and others] by intraperitoneal injection of radioactive gold in the white rat.) *Bull. Assoc., franç. l'étude cancer*, Oct.–Nov., 1956, *43*, 423–443. (From: Institut de Recherches sur le Cancer and Institut Gustave-Roussy—Centre clinique et thérapeutique, Paris, France.)

Referring to a previous publication by one of the authors (Harel) in which the production of hepatomas and extrahepatic cancers, with radioactivity in doses similar to those used in human therapy had been reported, the authors of this paper repeated these studies. They used intraperitoneal injections of radioactive gold in the white rat, with markedly prolonged duration of treatment and fractional injections of much higher doses, hoping to produce malignant tumors. One group of the animals was subjected to a hypoproteinic regime with the expectation of enhancing the production of hepatomas. The other group underwent a normal nutritional regime.

By the irradiation with radioactive gold, the authors produced a high number of cancers of the liver in animals in which spontaneous hepatomas, or even cholangiomas are unknown, and in which the development of malignant tumors of the liver even by injection of cancerogenic chemicals and thorotrast is very rare.—*Hans Lewin, M.D.*

MISCELLANEOUS

Ehrlich, Margarete. A photographic personnel dosimeter for x-radiation in the range from 30 kev. to beyond 1 mev. *Radiology*, April, 1957, *68*, 549–554. (From: The National Bureau of Standards, Washington, D. C.)

The author has constructed a photographic personnel dosimeter, the response of which approximates the biologic absorption of photon energy from 30 kev. to 1 mev. The "film-stack" principle was used and consisted of an insensitive film (Du Pont film type 606 in this instance) in each peripheral slot of the polyethylene container between which was the sensitive film (Du Pont 502) in the central tin-lead laminate case, there being three slots to the dosimeter.

The author's studies showed that this dosimeter was useful to interpret roentgen-ray exposures from 250 mr to 3 r with an acuracy of ± 20 per cent, and exposures from 3 r to 6 r with an accuracy of ± 30 per cent, no knowledge of photon energy being required; and if the photon energy were known to be in the million volt region, the range of the dosimeter could be extended to 600 r.—*Dean Nichols, M.D.*

WENDELL G. SCOTT